CSA716709
Organizacion y Digitalizacion CSA Ltda

Ops.

17757

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO
Organizacion y Digitalizacion CSA Ltda

PCT

SOLICITUD
PATENTE DE INVENCIÓN

EXPEDIENTE N° 09-17757

TITULO: INHIBIDORES DE LA METALOPROTEINASA MATRIZ

CLASIFICACION INTERNACIONAL: _____

SOLICITANTE: RANBAXY LABORATORIES LIMITED

DOMICILIO: INDIA

APODERADO: DARIO CARDENAS NAVAS

BOGOTÁ, D.C. _____

27-03-2004

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-017757- -00000-0000
Fecha: 2009-02-23 15:48:20 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 586

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

① **SOLICITUD DE:**

[X] Patente de Invención [ ] Patente de Modelo de Utilidad

[X] Capítulo I [ ] Capítulo II

② **SOLICITANTE**

Nombre: **Ranbaxy Laboratories Limited**
Dirección: Plot No 90 – Sector 32 Gurgaon, Haryyana 122001, India
Nacionalidad o Domicilio: India
Lugar de Constitución: India
Teléfono: 3137800 Fax: 3122410
E-mail: general@cardenasycardenas.com

IDENTIFICACION
[ ] NIT [ ] NIT
[ ] Otro [X] Otro
Cuál
Número

③ **REPRESENTANTE O APODERADO**

Nombre: **DARIO CARDENAS NAVAS**
Dirección: Carrera 7 No 71-52 Torre B Piso 9
Teléfono: 3137800 Fax: 3122410
E-Mail: **general@cardenasycardenas.com**

IDENTIFICACION
[X] NIT [ ] NIT
[ ] Otro [ ] Otro
Cual
Número 17066629 TP 1250
BTA C.S.J.

④ **INVENTOR(ES) (72)**

Nombre: VER ANEXO
Dirección: VER ANEXO
Nacionalidad o Domicilio: VER ANEXO

⑤ **PCT (86)**

Solicitud Internacional No. PCT/IB2007/053340 Fecha 21.08.2007
Publicación Internacional No. WO2008/023336 A2 Fecha 28.02.2008

⑥ **Título(54):**

INHIBIDORES DE LA METALOPROTEINASA MATRIZ

⑦ **Clasificación Internacional (51):**

⑧ **Prioridad**

SI [X] NO [ ]

(33)País de Origen	(32)Fecha	(31)N° de Solicitud
INDIA	22.08.2006	1880/DEL/2006

⑨ **Comprobante de Pago No.:** **09-14.393** **Fecha** **Febrero 23, 2009**

⑩ ANEXOS

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [X] Traducción de la solicitud internacional al castellano (Resumen, Resumen, descripción, reivindicaciones, dibujos)
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [X] 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.
- [X] Otros – Recibos oficiales por reivindicación de Reivindicación adicional 09-9,602 ; 09-6.557; 09-9.590

11 FIGURA CARACTERISTICA

12 Solicito la Concesión de la patente

NOMBRE: **DARIO CARDENAS NAVAS**

FIRMA:

C.C. 17066629 BTA TP. 1250 C.S.J.

④	Nombre:	1. Sattigeri Viswajanani Jitendra 2. Palle P. Vekata 3. Khera Manoj Kumar 4. Reddy Ranadheer 5. Tiwari Manoj Kumar 6. Soni Ajay 7. Rauf Abdul Rehman Abdul 8. Joseph Sony 9. Musib Arpita 10. Dastidar G. Sunanda 11. Srivastava Punit Kumar
INVENTOR(ES) (72)	Dirección:	1. N-323, Vijayrattan Vihar Gurgaon 122001 Haryana India 2. G901, Sylvan Heights Sanewadi Aundh, Pune 411007 Maharashtra, India 3. C-660/10, Krishna Colony Gurgaon 122001, Haryana, India 4. P.O. Thimmapuram (Mandal) Chievemula, Dist. Nalgonda, Suryapet 501213, Andhra Pradesh, India 5. Ravi Ranjan, Flat No 1, Shree Ram Apartment, Near Mawalni Church, Marwe Road, Malad (W) Mumbai 400095, Maharashtra, India 6. B-6 Om Vihar, Uttam Nagar, New Delhi 110059, India 7. Islampura, Post – Chandur-Biswa, Tahsil: Nandura, Distt. - Buldane, 443401, Maharashtra, India 8. Padayatty House, Thuravoor, P.O. Ernakulam – Dist. Kerala 683586, India 9. d/o Mr. P.L. Musib, Rabindra Sarani, Post- Khatra, District, Bankura West Bengal 722140,India 10. B-138, Sarita Vihar New Deli, 110044, India 11. 1263A, Sector 15 Part II, Gurgaon 122001, Haryana, India
	Nacionalidad o Domicilio:	1. HINDÚ 2. HINDÚ 3. HINDÚ 4. HINDÚ 5. HINDÚ 6. HINDÚ 7. HINDÚ 8. HINDÚ 9. HINDÚ 10. HINDÚ 11. HINDÚ

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 14,393
FECHA : FEBRERO 23 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-017757- -00000-0000

Fecha: 2009-02-23 15:48:20 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios. 586

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CARDENAS Y CARDENAS P.I. CONSIGNACION		BANCO DE BOGOTA	062754387	19780854	23/02/2009	7,196,800.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

CARDENAS Y CARDENAS
ABOGADOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 9,602
FECHA : FEBRERO 5 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-017757- -00000-0000

Fecha: 2009-02-23 15:48:20 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 586

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CARDENAS Y CARDENAS P.I.	CONSIGNACION	BANCO DE BOGOTA	062754387	105578163	05/02/2009	9,569,500.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	287,000.00
		TOTAL : $	287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-017757- -00000-0000
Fecha: 2009-02-23 15:48:20
Tra. 11 PATENTEIYII
Act. 411 PRESENTACION
Dep. 2020 NUECREACIONI
Eve: 378 FASENACIONALI
Folios: 586

RECIBO OFICIAL DE CAJA : 09 - 6,557
FECHA : ENERO 27 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CARDENAS Y CARDENAS P.I.	CONSIGNACION	BANCO DE BOGOTA	062754387	19780832	27/01/2009	12,686,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	21	CERTIFICACIONES	12,000.00
			TOTAL : $	12,000.00

SON: DOCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 9,590
FECHA : FEBRERO 5 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-017757- -00000-0000
Fecha: 2009-02-23 15:48:20 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 586

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CARDENAS Y CARDENAS P.I.	CONSIGNACION	BANCO DE BOGOTA	062754387	105578163	05/02/2009	9,569,500.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	1,000.00
		TOTAL : $	1,000.00

SON: MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION __X__ PCT ____ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ____

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional :

(71)Solicitante(s) RANBAXY LABORATORIES LIMITED

(72) Inventor(es)

1. Sattigeri Viswajanani Jitendra
2. Palle P. Vekata
3. Khera Manoj Kumar
4. Reddy Ranadheer (y otros)

(74) Apoderado: DARIO CARDENAS NAVAS

(30) Prioridad	(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
	1880/DEL/2006	**22.08.2006**	**India**

(85) Fecha inicio fase nacional: 21.03.2009

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 2007.08.21
No. de solicitud ***PCT/IB2007/053340***

(87) Publicación internacional
Fecha: ***28.02.2008***
N° publicación: ***WO2008/023336 A2***

(54) Titulo: **INHIBIDORES DE LA METALOPROTEINASA MATRIZ**

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMATICO

PATENTE DE INVENCION ____ PCT _X__ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL

(21) N° de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) RANBAXY LABORATORIES LIMITED

(72) Inventor(es)

1. Sattigeri Viswajanani Jitendra
2. Palle P. Vekata
3. Khera Manoj Kumar
4. Reddy Ranadheer (y otros)

(74) Apoderado: DARIO CARDENAS NAVAS

(30) Prioridad	(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
	1880/DEL/2006	**22.08.2006**	**India**

(85) Fecha límite inicio fase nacional: 21.03.2009
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 21.08.8007
No. de solicitud *PCT/IB2007/053340*

(87) Publicación internacional:
Fecha: ***28.02.2008***
No. Publicación WO2008/023336 A2

(54) Titulo: **INHIBIDORES DE LA METALOPROTEINASA MATRIZ**

(57) Resumen: El presente invento se relaciona con ácidos carboxílicos sustituidos mediante β-hidroxi y amino, que actúan como inhibidores de la metaloproteasa matriz, ácidos carboxílicos β-hidroxi diastereoméricamente puros, procesos correspondientes para la síntesis de composiciones farmacéuticas que contienen los compuestos del presente invento. Los compuestos del presente invento son útiles en el tratamiento de diversas enfermedades inflamatorias, de autoinmunidad y alérgicas, como ser los métodos para tratar el asma, la artritis reumatoidea, COPD, rinitis, osteoartritis, artritis soriásica, psoriasis, fibrosis pulmonar, desórdenes en la cura de heridas, inflamación pulmonar, síndrome de perturbación respiratoria agudo, periodontitis, esclerosis múltiple, gingivitis, ateroesclerosis, proliferación neointima, que lleva a la restenosis y a la insuficiencia cardíaca isquémica, ataque apopléjico, enfermedades renales, metástasis tumoral y otros desórdenes inflamatorios caracterizados por la hiper-expresión e hiper-activación de una metaloproteinasa matriz utilizando los compuestos.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud: 22) Fecha de solicitud: (30) Prioridad (31) ***No. Prioridad*** 32) ***Fecha*** (33) ***País*** **1880/DEL/2006** **22.08.2006** **India**	(51) Int Cl: (71)Solicitante(s) **RANBAXY LABORATORIES** (72) Inventor(es) 1. Sattigeri Viswajanani Jitendra 2. Palle P. Vekata 3. Khera Manoj Kumar 4. Reddy Ranadheer (y otros) (74) Apoderado: **DARIO CARDENAS NAVAS**
(85) Fecha limite inicio fase nacional: *21.03.2009* (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: *21.08.2007* No. de solicitud PCT/IB2007/053340	(87) Publicación internacional Fecha: *28.02.2008* N° publicación: ***WO 2008/023336 A2***
(54) Titulo: **INHIBIDORES DE LA METALOPROTEINASA MATRIZ**	

Resumen:

El presente invento se relaciona con ácidos carboxílicos sustituidos mediante β-hidroxi y amino, que actúan como inhibidores de la metaloproteasa matriz, ácidos carboxílicos β-hidroxi diastereoméricamente puros, procesos correspondientes para la síntesis de composiciones farmacéuticas que contienen los compuestos del presente invento. Los compuestos del presente invento son útiles en el tratamiento de diversas enfermedades inflamatorias, de autoinmunidad y alérgicas, como ser los métodos para tratar el asma, la artritis reumatoidea, COPD, rinitis, osteoartritis, artritis soriásica, psoriasis, fibrosis pulmonar, desórdenes en la cura de heridas, inflamación pulmonar, síndrome de perturbación respiratoria agudo, periodontitis, esclerosis múltiple, gingivitis, ateroesclerosis, proliferación neointima, que lleva a la restenosis y a la insuficiencia cardíaca isquémica, ataque apopléjico, enfermedades renales, metástasis tumoral y otros desórdenes inflamatorios caracterizados por la hiper-expresión e hiper-activación de una metaloproteinasa matriz utilizando los compuestos.

APOSTILLE

00517

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY: MICHELLE MORGAN
3. ACTING IN THE CAPACITY OF: NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF: MICHELLE MORGAN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 27TH DAY OF SEPTEMBER 2007
7. BY: Michellene Davis, NEW JERSEY TREASURER
8. NO. A304221
9. SEAL/STAMP:
10. SIGNATURE

Coop Notario 16 para constar que esta copia corresponde con documento original presentado para su autenticación en Bogotá, D.C. - República de Colombia

20 FEB 2009

JAIRO MARTINEZ GONZALEZ
NOTARIO 16 ENCARGADO

Colombia -

POWER OF ATTORNEY

In the city of Princeton, NJ USA on the 21st day of the month of September, two thousand seven (2007) before me, Michelle Morgan, Notary Public, appeared Mr. Jay R. Deshmukh of age, and domiciled at c/o Ranbaxy Inc., 600 College Road East, Suite 2100, Princeton, NJ 08540 USA, and stated:

FIRST: That he/she acts in his/her capacity of Senior Vice President - Intellectual Property of **Ranbaxy Laboratories Limited,** a company legally constituted and in existence in accordance with the laws of **India** and domiciled at **Plot No. 90 – Sector 32 Gurgaon, Haryana 122001, India**; as evidenced in the By Laws, documents which I have examined.

SECOND: That in such capacity he/she grants hereby special, ample and sufficient Power of Attorney to DARIO CARDENAS-NAVAS and/or EDUARDO CARDENAS-CABALLERO and/or BERNARDO P. CARDENAS-MARTINEZ y/o JAMES VALDIRI-REYES and/or LUZ HELENA ADARVE-GOMEZ and/or JUANITA ACOSTA GÓMEZ and/or ANA MARIA RUIZ RUEDA, registered lawyers of the firm CARDENAS & CARDENAS-LAWYERS, domiciled at Carrera 7 No. 71-52, Torre B, Piso 9 Bogotá, D.C., Colombia, to carry before the corresponding Colombian national Offices and authorities the proceedings to obtain trademarks, patents, utility models, industrial drawings and designs, deposits of commercial names and ensigns, as well as processing of renewals, assignments, change of name or domicile of the owner, cancellation actions, waivers and licenses of the same for which purpose they are empowered to take before said authorities all necessary actions for the indicated purposes; to file applications, statements, claims, formulate descriptions, amendments, oppositions and appeals; pay all taxes and installments and make any other payments determined by law; to receive every document and values issuing the respective discharge; to fulfill any other requirements and take, in general, every measure that they shall deem opportune for the defense and protection of the Industrial Property of the company in the event of infringements, oppositions, proceedings for cancellation or annulment, imposition of fines, passing the antecedents to the courts; they are empowered to appear as plaintiff or defendant before the competent judges, being entitled to transact, submit to arbitration, waive, receive, resign, withdraw, appeal, ratify and all other legal powers which may be necessary, and it is hereby declared ever since now valid and good whatever such attorneys do for its benefit, granting them also power to substitute this proxy and if necessary to revoke such substitutions.

THIRD: That for purposes of articles 597 and 543 of the Colombian code of Commerce the attorneys are empowered to receive service of notice and designate judicial and extrajudicial attorneys.

SIGNED AT Princeton, NJ USA ON September 21, 2007

BY _____ Jay R. Deshmukh

Michelle Morgan NOTARY PUBLIC

(LEGALIZATION BY COLOMBIAN CONSUL IS REQUIRED OR BY APOSTILLE)

MICHELLE MORGAN
NOTARY PUBLIC OF NEW JERSEY
ID NO 2323888
MY COMMISSION EXPIRES JANUARY 7, 2010

Coop Notario 16 para constar que esta copia corresponde con documento original presentado para su autenticación en Bogotá, D.C. - República de Colombia

20 FEB 2009

JAIRO MARTINEZ GONZALEZ
NOTARIO 16 ENCARGADO

The undersigned Notary Public certifies that Mr. Jay R. Deshmukh appeared before me and signed the preceding document; that I know him personally and I am certain that he has legal capacity to grant it; that he is Senior Vice President – Intellectual Property of **Ranbaxy Laboratories Limited,** and is consequently authorized to grant such document; that such company is organized under the laws of **India**, and is domiciled at **Plot No. 90 – Sector 32 Gurgaon, Haryana 122001, India**; and that the act for which this document is granted is included among those which constitute the corporate object of the named company. Furthermore, that such company performs its corporate purpose in accordance with the laws of its incorporation and domicile.

I am certain of all these facts because I have examined the respective documents consisting of Power of Attorney all of which I hereby attest.

MICHELLE MORGAN
NOTARY PUBLIC OF NEW JERSEY
ID NO 2323686
MY COMMISSION EXPIRES JANUARY 7, 2010

NOTARY PUBLIC (signature)
Issued and signed in PRINCETON, NJ USA
Dated SEPTEMBER 21, 2007

(LEGALIZATION BY COLOMBIAN CONSUL IS REQUIRED OR BY APOSTILLE)

Corpo Notario 16 (E) del Circulo de Bogotá, hago constar que esta copia, coincide con documento original presentado para su autenticación
Bogotá, D.C. - República de Colombia
20 FEB 2009
JHON JAIRO MARTINEZ GONZALEZ
NOTARIO 16 ENCARGADO

RANBAXY

CORPORATE OFFICE : PLOT NO. 90, SECTOR-32, GURGAON-122001 (HARYANA), INDIA
PHONE : +91-124-5135000 FAX : +91-124-5135001

February 3, 2006

TO WHOM SOEVER IT MAY CONCERN

This is to certify that the address of the Corporate Office of Ranbaxy Laboratories Ltd. has been changed as given below :

Ranbaxy Laboratories Ltd.
Plot No. 90, Sector 32
Gurgaon-122001
(Haryana), India.

for RANBAXY LABORATROIES LTD.

(S.K. PATAWARI)
COMPANY SECRETARY

D. N. SUHAG
GURGAON
D-1512

ATTESTED
A TRUE COPY
(D. N. SUHAG)
ADVOCATE & NOTARY PUBLIC
GURGAON (HARYANA)

Corpo Notario 16 (E) del Circulo de Bogotá, hago constar que esta copia, coincide con documento original presentado para su autenticación
Bogotá, D.C. - República de Colombia
20 FEB 2009
JHON JAIRO MARTINEZ GONZALEZ
NOTARIO 16 ENCARGADO

RANBAXY LABORATORIES LIMITED
REGISTERED OFFICE : SAHIBZADA AJIT SINGH NAGAR - 160 055, DISTT. ROPAR (PUNJAB)
WEBSITE http://www.ranbaxy.com

Martha S. Sarmiento S.
Martha S. Sarmiento S.
Traductora Oficial Juramentada
Resolución No. 835 Minjusticia

TRADUCCIÓN OFICIAL DE LOS SIGUIENTES DOCUMENTOS: APOSTILLA DE LA CONVENCIÓN DE LA HAYA No. A304221, con fecha del 27 de Septiembre de 2007, firmada por Michellene Davis. PODER DE ABOGADO otorgado por la Compañía Ranbaxy Laboratories Ltd., a la Firma de Abogados Cárdenas y Cárdenas, de Bogotá, Colombia, firmado por Jay R. Deshmukh, Vicepresidente principal de dicha Compañía en la ciudad de Princeton, NJ y fue autenticado ante Michelle Morgan, Notario Público del Estado de New Jersey el día 21 de septiembre de 2007. CERTIFICACIÓN NOTARIAL expedida y firmada por Michelle Morgan, Notario Público del Estado de New Jersey, el 21 de septiembre de 2007. CERTIFICADO DE CAMBIO DIRECCIÓN de la compañía Ranbaxy Laboratories Ltd., con fecha del 3 de febrero de 2006 y firmada por S.K. Patawari – Secretario.

Traducción realizada por Martha Sofía Sarmiento Solano, Traductora e Intérprete Oficial Español – Inglés - Español, nombrada para el cargo mediante Resolución del Ministerio de Justicia, Nº 835, del 3 de mayo de 1988.

Apostilla

(Convención de La Haya, 5 de octubre de 1961)

1. País:	**Estados Unidos de América**	
2. Este documento Público ha sido firmado por:	**MICHELLE MORGAN**	
3. actuando en calidad de	**NOTARIO PÚBLICO DE NEW JERSEY**	
4. Lleva el sello / estampilla de	**MICHELLE MORGAN, NOTARIO**	

CERTIFICADO

5. En:	**TRENTON, NEW JERSEY**	
6. El:	**27 DE SEPTIEMBRE DE 2007**	
7. Por:	**MICHELLENE DAVIS, TESORERO, EN NEW JERSEY**	
8. Bajo el número:	**A304221**	
9. Lleva Sello / Estampilla:	**SELLO DEL ESTADO DE NEW JERSEY**	
10. Firmado por:	**Firma autógrafa**	

MINISTERIO DE RELACIONES EXTERIORES
2007 OCT 30 P 2:13
JEFE DE LEGALIZACIONES BOGOTA D.C.
NO SE ASUME RESPONSABILIDAD DEL TEXTO
680102
FUNCIONES DELEGADAS

Corap Notario 16 (E) del Circulo de Bogotá, hago constar que esta copia, coincide con el documento original presentado para su autenticación en Bogotá, D.C. - República de Colombia
20 FEB 2009
JHON JAIRO MARTINEZ GONZALEZ
NOTARIO 16 ENCARGADO

Martha S. Sarmiento S.
Martha S. Sarmiento S.
Traductora Oficial Juramentada
Resolución No. 835 Minjusticia

COLOMBIA -

PODER DE ABOGADO

En la ciudad de Princeton, NJ, Estados Unidos de América a los 21 días del mes de Septiembre del año dos mil siete (2007) ante mí, Michelle Morgan, Notario Público, compareció el señor Jay R. Deshmukh, mayor de edad, y domiciliado en c/o Ranbaxy Inc., 600 College Road East, Suite 2100, Princeton, NJ 08540 Estados Unidos de América, quien declaró lo siguiente:

PRIMERO: Que él/ella actúa en calidad de Vicepresidente principal – Propiedad Intelectual de **Ranbaxy Laboratories Limited**, una Compañía legalmente constituida que opera según las leyes de **la India** y cuyo domicilio es **Plot No. 90 – Sector 32 Gurgaon, Haryana 122001, India**; de acuerdo con los estatutos y documentos que he examinado.

SEGUNDO: Que haciendo uso de las facultades del cargo arriba mencionado, él/ella otorga Poder de Abogado, especial, amplio y suficiente a DARÍO CÁRDENAS NAVAS, y/o a EDUARDO CÁRDENAS CABALLERO, y/o a BERNARDO P. CÁRDENAS MARTÍNEZ, y/o a JAMES VALDIRI REYES, y/o a LUZ HELENA ADARVE GÓMEZ, y/o a JUANITA ACOSTA GÓMEZ, y/o a ANA MARÍA RUIZ RUEDA, abogados registrados quienes trabajan para la firma CÁRDENAS & CÁRDENAS ABOGADOS, con sede en la Carrera 7 No. 71-52, Torre B, Piso 9, en Bogotá, D.C., Colombia, para que gestionen en Colombia ante las Oficinas y Autoridades correspondientes la obtención de marcas registradas, patentes, modelos de utilidad, dibujos y diseños industriales, depósitos de nombres y enseñas comerciales, como también para el procesamiento de renovaciones, cesiones, cambios de nombre o domicilio del titular, cancelación de acciones, renuncias y licencias de las mismas, propósitos para los cuales se les otorga poder para que lleven a cabo ante dichas autoridades todas las acciones necesarias para los propósitos indicados, como radicar solicitudes, hacer

Corap Notario 16 (E) del Circulo de Bogotá, hago constar que esta copia, coincide con el documento original presentado para su autenticación en Bogotá, D.C. - República de Colombia
20 FEB 2009
JHON JAIRO MARTINEZ GONZALEZ
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declaraciones, reclamaciones, formular descripciones, realizar enmiendas o modificaciones, interponer recursos de oposición y apelaciones; pagar todos los impuestos y cuotas y hacer cualquier otro pago establecido por ley; recibir todos los documentos y dineros y emitir el descargo correspondiente; cumplir con cualquier otro requerimiento y tomar, en general, todas las medidas que consideren oportunas para defender y proteger la Propiedad Industrial de la Compañía en el evento de infracciones, oposiciones, reclamaciones, para cancelación o anulación, imposición de sanciones, presentar antecedentes ante las Cortes y Tribunales. Además, quedan facultados para comparecer como demandantes o demandados ante jueces competentes, también se les da poder para negociar, solicitar arbitraje, ceder, recibir, dimitir, rescindir o desistir, apelar, ratificar y todos los poderes legales adicionales que sean necesarios. También se declara que a partir de ahora todas las acciones que realicen dichos abogados respaldando este Poder de representación son buenas y válidas. Adicionalmente se les otorga facultades para sustituir este Poder y si es necesario revocar dichas sustituciones.

TERCERO: Con el propósito de cumplir con los artículos 597 y 543 del Código Colombiano de Comercio, dichos abogados quedan facultados para recibir notificaciones judiciales y designar abogados judicial y extrajudicialmente.

FIRMADO EN Princeton, NJ, ESTADOS UNIDOS DE AMÉRICA,
el 21 de Septiembre de 2007.

Por: Firma Autógrafa, Jay R. Deshmukh

Michelle Morgan NOTARIO PÚBLICO

Firma Autógrafa y Sello:

MICHELLE MORGAN
NOTARIO PÚBLICO DE NEW JERSEY
ID NO 2323686
MI COMISIÓN FINALIZA EL 7 DE ENERO DE 2010

(Este documento se debe legalizar ante el Cónsul Colombiano o a través de Apostilla)

Consulado Notario 16 (E) del Circuito de Bogotá, hago constar que esta copia, coincide con documento original presentado para su autenticación
Bogotá, D.C. - República de Colombia
20 FEB 2009
JHON JAIRO MARTINEZ GONZALEZ
NOTARIO 16 ENCARGADO

Martha L. Sarmiento L.
Martha L. Sarmiento L.
Traductora Oficial Juramentada
Resolución No. 835 Minjusticia

El suscrito Notario Público certifica que el Señor Jay R. Deshmukh compareció ante mí y firmó el documento anterior, que lo conozco personalmente y estoy seguro que él tiene la facultad legal para otorgarlo. Que él es el Vicepresidente principal – Propiedad Intelectual de la Compañía **Ranbaxy Laboratories Limited**, y por consiguiente está autorizado para expedir y otorgar dicho documento. Que dicha compañía está organizada y se rige por las leyes de **la India**, cuya sede se encuentra ubicada en **Plot No. 90 – Sector 32 Gurgaon, Haryana 122001, India**. Además certifico que el acto a través del cual se expide y otorga este documento incluye los que constituyen el objeto corporativo de la mencionada Compañía. Como también certifico que dicha compañía desarrolla su propósito corporativo de acuerdo con las leyes de su incorporación y domicilio.

Tengo la certeza sobre la veracidad de todos estos hechos debido a que examiné el Poder de Abogado. Doy testimonio de todo lo anterior.

Por: Firma Autógrafa
NOTARIO PÚBLICO (firma)

MICHELLE MORGAN
NOTARIO PÚBLICO DE NEW JERSEY
ID NO 2323686
MI COMISIÓN FINALIZA EL 7 DE ENERO DE 2010

Expedido y firmado en **Princeton, NJ, ESTADOS UNIDOS DE AMÉRICA**
Fecha: **21 de Septiembre de 2007**

(Este documento se debe legalizar ante el Cónsul Colombiano o a través de Apostilla)

Consulado Notario 16 (E) del Circuito de Bogotá, hago constar que esta copia, coincide con documento original presentado para su autenticación
Bogotá, D.C. - República de Colombia
20 FEB 2009
JHON JAIRO MARTINEZ GONZALEZ
NOTARIO 16 ENCARGADO

RANBAXY

CORPORATE OFFICE : PLOT NO. 90, SECTOR 32, GURGAON-122001 (HARYANA), INDIA
PHONE : +91-124 5135000 FAX : +91-124-5135001

3 de febrero de 2006

A QUIEN LE PUEDA INTERESAR

Con la presente certificamos que la dirección de la Oficina Corporativa de Ranbaxy Laboratories Ltd. ha cambiado por la que se suministra a continuación:

Ranbaxy Laboratories Limited.
Plot No. 90 – Sector 32
Gurgaon - 122001
(Haryana), India

Por Ranbaxy Laboratories Ltd,

Firma autógrafa
(S.K. PATAWARI)
SECRETARIO DE LA COMPAÑIA

CERTIFICADA COMO COPIA VERDADERA

Abogado y Notario Público de Gurgaon (Haryana)
4 de Febrero de 2006

RANBAXY LABORATORIES LIMITED
REGISTERED OFFICE SAHIBZADA AJIT SINGH NAGAR - 160 055, DISTT. ROPAR (PUNJAB)
WEBSITE http://www.ranbaxy.com

CERTIFICO QUE ESTA ES UNA TRADUCCIÓN FIEL DEL INGLÉS AL ESPAÑOL DE LOS DOCUMENTOS QUE HE TENIDO A LA VISTA; QUE SOY TRADUCTORA E INTERPRETE OFICIAL ACREDITADA POR RESOLUCIÓN Nº 835 DEL 3 DE MAYO DE 1988 DEL MINISTERIO DE JUSTICIA Y QUE ESTOY REGISTRADA ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE COLOMBIA.

Bogotá, 26 de Octubre de 2007

Martha S. Sarmiento S.
Traductora Oficial Juramentada
Resolución No. 835 Minjusticia

Consulado 16 (E) del Circulo de Bogotá, hago constar que esta copia, coincide con el documento original presentado para su autenticación. Bogotá, D.C. - República de Colombia
20 FEB 2009
JHON JAIRO MARTINEZ GONZALEZ
NOTARIO 16 ENCARGADO

Docket No. RLL-895

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/IB2007/053340
- __ Other (specify) ____ _____ _____ _____ ____

Title of the Invention:

MATRIX METALLOPROTEINASE INHIBITORS

Inventors (assignors)

Name	Address
Viswajanani J. SATTIGERI	N-323, Vijayrattan Vihar 122001 Gurgaon, Haryana INDIA
Venkata P. PALLE	G901, Sylvan Heights Sanewadi, Aundh 411007 Pune, Maharashtra INDIA
Manoj Kumar KHERA	C-660/10, Krishna Colony 122001 Gurgaon, Haryana INDIA
Ranadheer REDDY	P.O. Thimmapuram (Mandal) Chievemula Dist., Nalgonda 501213 Suryapet, Andhra Pradesh INDIA

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Manoj Kumar TIWARI	c/o Ravi Ranjan Flat No. 1, Shree Ram Apartment, Near Mawalni Church, Marwe Road, Malad (W) 400095 Mumbai, Maharashtra INDIA
Ajay SONI	B-6 Om Vihar, Uttam Nagar 110059 New Delhi, Delhi INDIA
Abdul Rehman Abdul RAUF	Islampura, Post – Chandur-Biswa, Tahsil: Nandura, Distt. 443401 Buldane, Maharashtra INDIA
Sony JOSEPH	Padayatty House, Thuravoor 683586 Ernakulam, Kerala INDIA
Arpita MUSIB Arpita Musib	d/o Mr. P.L. Musib, Rabindra Sarani Post-Khatra, District 722140 Bankura, West Bengal INDIA
Sunanda G. DASTIDAR	B-138, Sarita Vihar 110044 New Delhi, Delhi INDIA
Punit Kumar SRIVASTAVA	1263A, Sector 15, Part II 122001 Gurgaon, Haryana 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;

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
Viswajanani J. SATTIGERI	Viswajanani J.S.	10/9/07
Venkata P. PALLE	P.V.P. Acharyulu	21/01/08
Manoj Kumar KHERA	Manoj Kh	10/09/07
Ranadheer REDDY	B.R.Reddy	10/09/07
Manoj Kumar TIWARI	M.Tiwari	11/01/2008
Ajay SONI	A.T.Soni	10-9-2007
Abdul Rehman Abdul RAUF	A.R.Rauf	10/09/07
Sony JOSEPH	Sony Joseph	10/9/07
Arpita MUSIB	Arpita Musib	06/09/07
Sunanda G. DASTIDAR	Sunanda	31/8/07
Punit Kumar SRIVASTAVA	Punit	31/8/07

INTELLECTUAL PROPERTY INDIA

सत्यमेव जयते

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI
BOUDHIK SAMPADA BHAWAN,
PLOT NO. 32, SECTOR – 14,
NEW DELHI - 110 075.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application and Provisional Specification*** *filed in connection with Patent Application No.* ***1880/DEL/2006*** *dated* ***22nd August 2006.***

Witness my hand this 17th day of September 2007.

(Dr. Rajesh Dixit)
Assistant Controller of Patents & Designs

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1880 DEL 06

FORM 1 THE PATENT ACT 1970 (39 of 1970) & The Patents Rules, 2003 APPLICATION FOR GRANT OF PATENT (See section 7, 54 and 135 and Rule 20(1)	(FOR OFFICE USE ONLY) 22 AUG 2006 Application No._____ Filing Date:_____ Amount of Fee Paid: Rs._____ CBR No. _____ Signature: _____

1. APPLICANT (S)
RANBAXY LABORATORIES LIMITED, an Indian Company, incorporated under the Companies Act, 1956, Head Office at 12th Floor, Devika Tower, 6, Nehru Place, New Delhi-110019, India.

2. INVENTOR (S)
VISWAJANANI JITENDRA SATTIGERI, VENKATA P PALLE, MANOJ KUMAR KHERA, RANADHEER REDDY, MANOJ KUMAR TIWARI, AJAY SONI, SUNANDA G. DASTIDAR, PUNIT KUMAR SRIVASTAVA,
All Indian Nationals, of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon – 122001, Haryana, India.

3. TITLE OF THE INVENTION
"MATRIX METALLOPROTEINASE INHIBITORS"

4. ADDRESS FOR CORRESPONDENCE OF APPLICANT/ AUTHORIZED AGENT IN INDIA:
DR. B. VIJAYARAGHAVAN
Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No. 20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon–122001, Haryana, India.
Telephone Nos.: (0124) 2343126, 4194271
Fax Nos. (0124) 2342027, 4016855

5. PRIORITY PARTICULARS OF THE APPLICATION(S) FILED IN CONVENTION COUNTRY: NOT APPLICABLE

6. PARTICULARS FOR FILING PATENT COOPERATION TREATY (PCT) NATIONAL PHASE APPLICATION:

7. PARTICULARS FOR FILING DIVISIONAL APPLICATION: NOT APPLICABLE

8. PARTICULARS FOR FILING PATENT OF ADDITION: NOT APPLICABLE

9. **DECLARATIONS:**

(i) **Declaration by the Inventor(s):**

We, the above named inventor(s) is/are the true and first inventor(s) for this invention and declare that the applicant herein, **Ranbaxy Laboratories Limited**, Head Office at 12th Floor, Devika Tower, 6, Nehru Place, New Delhi-110019, India, is our assignee or legal representative.

Date	Signature(s)	Name (s)
_____	_____	**Viswajanani Jitendra Sattigeri**
_____	_____	**Venkata P Palle**
_____	_____	**Manoj Kumar Khera**
_____	_____	**Ranadheer Reddy**
_____	_____	**Manoj Kumar Tiwari**
_____	_____	**Ajay Soni**
_____	_____	**Sunanda G. Dastidar**
_____	_____	**Punit Kumar Srivastava**

(ii) **Declaration by the applicant(s) in the convention country:**

We, the applicant, in the convention country declare that the applicant herein is our assignee or legal representative.

For Ranbaxy Laboratories Limited

Date : _____

(SUSHIL KUMAR PATAWARI)
Company Secretary

(iii) **Declaration by the Applicant(s) :**

We, the applicant (s) hereby declare (s) that :-

- ◊ We are in possession of the above-mentioned invention.
- ◊ The provisional / complete specification relating to the invention is filed with this application.
- ◊ The invention as disclosed in the specification uses the biological material from India and necessary permission from the competent authority shall be submitted by us before the grant of the patent to us.
- ◊ There is no lawful ground of objection to the grant of the Patent to us.
- ◊ We are the assignee or legal representative of true and first inventors.
- ◊ The application or each of the applications, particulars of which are given in Para-5 was the first application in convention country / countries in respect of our invention.
- ◊ We claim the priority from the above mentioned application(s) filed in convention country/ countries and state that no application for protection in respect of the invention had been made in a convention country before that date by us or by any person from which we derive the title.
- ◊ Our application in India is based on International application under Patent Cooperation Treaty (PCT) as mentioned in Para-6.

◊ The application is divided out of our application particulars of which are given in Para-7 and pray that this application may be treated as deemed to have been filed on _____ under sec.16 of the Act.

◊ The said invention is an improvement in or modification of the invention particulars of which are given in Para-8.

10. **FOLLOWING ARE THE ATTACHMENTS WITH THE APPLICATION:**

(a) Provisional specification / Complete specification
(b) Complete specification (in conformation with the international applications)/as amended before the International Preliminary Examination Authority (IPEA), as applicable (2 copies), No. of Pages _____ No. of claims _____.
(c) Drawings (in conformation with the international application)/as amended before the International Preliminary Examination Authority (IPEA), as applicable (2 copies), No. of sheets _____.
(d) Priority documents
(e) Translation of priority documents / Specification/International Search Report
(f) Statement and undertaking on Form 3
(g) Power of Authority
(h) Declaration of inventorship on Form 5
(i) Sequence listing in electronic form
(j) _____

Fee Rs. _____ in Cash/Cheque/Bank Draft bearing No. _____

Date _____ on HDFC Bank Limited, Gurgaon.

We hereby declare that to the best of our knowledge, information and belief the fact and matters stated herein are correct and we request that a patent may be granted to us for the said invention.

Dated this the 18TH day of August, 2006.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

To

The Controller of Patent
The Patent Office
New Delhi

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FORM 2 1880 DEL 06

The Patents Act, 1970

(39 of 1970

&

The Patent Rule, 2003)

22 AUG 2006

PROVISIONAL SPECIFICATION

(See Section 10)

MATRIX METALLOPROTEINASE INHIBITORS

DUPLICATE

RANBAXY LABORATORIES LIMITED

HEAD OFFICE : 12TH FLOOR, DEVIKA TOWER,

06, NEHRU PLACE, NEW DELHI – 110019

(A Company incorporated under the Companies Act, 1956)

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

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Field of the Invention

The present invention relates to certain β-hydroxy and amino substituted carboxylic acids as matrix metalloprotease inhibitors, particularly diastereomerically pure β-hydroxy carboxylic acids 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, perodontitis, 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.

Background of the Inventions

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

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

MMP-12 also known as macrophage elastase or metalloelastase is expressed in activated macrophages and has been shown to be secreted from alveolar macrophages from smokers as well as in foam cells in atherosclerotic lesions. MMP-12 knockout mouse studies have shown the development of significant emphysema, thus supporting its role in COPD. MMP-9 (gelatinase B, 92 kDa type IV collagenase) is one member of the MMP family that is released as a proenzyme and subsequently activated via a protease cascade in vivo. The concentration of MMP-9 is increased in diseases like asthma, interstitial pulmonary fibrosis (IPF), adult

respiratory distress syndrome (ARDS), and in chronic obstructive pulmonary disease (COPD). Because of its proteolytic ability, MMP-9 has been implicated in tissue remodelling of the airways and lungs in chronic inflammatory diseases such as severe asthma and COPD. MMP-9 is also likely to be physiologically important because of its ability to regulate the digestion of components of the extracellular matrix as well as the activity of other proteases and cytokines. MMP-9 is secreted in neutrophils, macrophages, osteoclasts, which are easily induced by cytokines and growth factors, and plays a role in various physiological and pathological processes.

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

Examples of inflammatory conditions and autoimmune disorders in which the compounds of the invention have potentially beneficial effects include diseases of the respiratory tract such as asthma (including allergen-induced asthmatic reactions), cystic fibrosis, bronchitis (including chronic bronchitis), chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), chronic pulmonary inflammation, rhinitis and upper respiratory tract inflammatory disorders (URID), ventilator induced lung injury, silicosis, pulmonary sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, arthritis e.g. rheumatoid arthritis, osteoarthritis, infectious arthritis, psoriasis arthritis, traumatic arthritis, rubella arthritis, Reiter's syndrome, gouty arthritis and prosthetic joint failure gout acute synovitis, spondylitis and non-articular inflammatory conditions, e.g. herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitic fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, inflammatory disorders of the gastrointestinal tract, e.g. ulcerative colitis, diverticulitis, Crohn's disease, inflammatory bowel diseases, irritable bowel syndrome and gastritis, multiple sclerosis, systemic lupus erythematosus scleroderma, autoimmune exocrinopathy, autoimmune encephalomyelitis, diabetes, tumor angiogenesis and metastasis, cancer including carcinoma of the breast, colon, rectum, lung, kidney, ovary, stomach, uterus, pancreas, liver, oral, laryngeal and prostate, melanoma, acute and chronic leukemia, periodontal disease, neurodegenerative disease Alzheimer's disease, Parkinson's disease, epilepsy, muscle degeneration, inguinal hernia retinal degeneration, diabetic retinopathy, macular degeneration, ocular inflammation, bone desorption diseases, osteoporosis, osteopetrosis, graft vs. host reaction allograft rejections, sepsis, endotoxemia, toxic shock syndrome, tuberculosis, usual interstitial and cryptogenic organizing pneumonia, bacterial meningitis, systemic cachexia, cachexia secondary to infection

or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), malaria, leprosy, leishmaniasis, Lyme disease, glomerulonephritis, glomerulosclerosis, renal fibrosis, liver fibrosis, pancreatitis, hepatitis, endometriosis, pain, e.g. that associated with inflammation and/or trauma, inflammatory diseases of the skin, e.g. dermatitis, 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).

WO2004/110974 discloses compounds and their physiologically functional derivatives as inhibitors of matrix metalloproteinase enzymes. WO2004/113279 discloses inhibitors of matrix metalloproteinase. US6350885 discloses tricyclic heteroaromatic compounds and their derivatives as inhibitors of matrix metalloproteinases. WO9809940 discloses biphenyl butyric acids and their derivatives as inhibitors of matrix metalloproteinases. Journal of Medicinal Chemistry, 1968, vol. 11(6), 1139-1144 discloses synthesis and anti-inflammatory activity of 4-(p-biphenylyl)-3-hydroxybutyric acid and related compounds. WO 96/15096 discloses substituted 4-biarylbutyric or 5-biarylpentanoic acids and derivatives as matrix metalloproteinase inhibitors.

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.

SUMMARY OF THE INVENTION

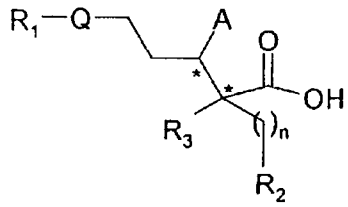
In one aspect, there are provided matrix metalloprotease inhibitors, which can be useful as safe and effective therapeutic or prophylactic agents for the treatment of various inflammatory and allergic diseases. Also provided are processes for synthesizing such compounds.

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 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, diastereomers, conformational isomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier and optionally included excipients.

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

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



Formula I

wherein

* denotes stereogenic (asymmetric) centre of defined configuration;

n is an integer from 1 to 5;

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R_1 is hydrogen or 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, $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$.

Q is optionally substituted aryl or heteroaryl.

In one embodiment, the invention encompasses compounds that include, for example

(2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4-pyrimidin-5-ylphenyl)pentanoic acid (Compound No.1),
(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-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 2),
(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. 3),
(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. 4),
(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. 5),
(2*S*,3*R*)-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 6),
(2*S*,3*R*)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 7),
(2*S*,3*R*)-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. 8),
(2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 9),
(2*S*,3*R*)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 10),
(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 11),
(2*S*,3*R*)-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. 12),
(2*S*,3*R*)-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. 13),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 14),
(2*S*,3*R*)-5-(4'-chloro-3'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 15),

(2*S*,3*R*)-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. 16),
(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. 17),
(2*S*,3*R*)-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. 18),
(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. 19),
(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. 20),
(2*S*,3*R*)-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. 21),
(2*S*,3*R*)-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. 22),
(2*S*,3*R*)-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. 23),
(2*S*,3*R*)-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. 24),
(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 25),
(2*S*,3*R*)-5-(4'-ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 26),
(2*S*,3*R*)-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. 27),
(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 28),
(2*S*,3*R*)-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. 29),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 30),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyridin-3-ylphenyl)pentanoic acid (Compound No. 31),
(2*S*,3*R*)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 32),
(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 33),
(2*S*,3*R*)-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 34),
(2*S*,3*R*)-3-hydroxy-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 35),
(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 36),
(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 37),
(2*S*,3*R*)-3-hydroxy-2-{2-[7-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 38),
(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 39),
(2*S*,3*R*)-2-[2-(8-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 40),
(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 41),

(2*S*,3*R*)-3-hydroxy-2-{2-[5-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 42),
(2*S*,3*R*)-5-(4'-chloro-3'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 43),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-isobutyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 44),
(2*S*,3*R*)-5-biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 45),
(2*S*,3*R*)-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. 46),
(2*S*,3*R*)-5-(3,3'-difluoro-4'-methoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 47),
(2*S*,3*R*)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 48),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1*H*-tetrazol-1-yl)phenyl]pentanoic acid (Compound No. 49),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 50),
(2*S*,3*R*)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 51),
(2*S*,3*R*)-3-hydroxy-5-[4-(1-isobutyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 52),
(2*S*,3*R*)-5-biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 53),
(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 54),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 55),
(2*S*,3*R*)-5-(4'-chloro-3-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 56),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[6-(4-methoxyphenyl)pyridin-3-yl]pentanoic acid (Compound No. 57),
(2*S*,3*R*)-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. 58),
(2*S*,3*R*)-5-[6-(4-chlorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 59),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 60),
(2*S*,3*R*)-5-[4-(4-chlorophenyl)-2-thienyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 61),
(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)-2-thienyl]pentanoic acid (Compound No. 62),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-{4-[4-(trifluoromethyl)phenyl]-2-thienyl}pentanoic acid (Compound No. 63),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-(3-fluoro-4-methoxyphenyl)-2-thienyl]-3-hydroxypentanoic acid (Compound No. 64),
(2*S*,3*R*)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 65),
(2*S*,3*R*)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 66),
(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 67),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 68),
(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 69),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[2-fluoro-5-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 70),
(2*S*,3*R*)-5-(4'-chloro-4-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 71),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[6-fluoro-4'-(trifluoromethyl)biphenyl-3-yl]-3-hydroxypentanoic acid (Compound No. 72),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-fluoro-3-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 73),
(2*S*,3*R*)-5-(4'-chloro-6-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 74),
(2*S*,3*R*)-5-(3',6-difluoro-4'-methoxybiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 75),
(2*S*,3*R*)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 76),
(2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 77),
(2*S*,3*R*)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 78),
(2*S*,3*R*)-2-[2-(5-chloro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 79),
(2*S*,3*R*)-2-[2-(4-fluoro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 80),
(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 81),
(2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid (Compound No. 82),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-phenylpentanoic acid (Compound No. 83),
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4 (trifluoromethyl)phenyl]pentanoic acid (Compound No. 84),
(2*S*,3*R*)-5-(4-*tert*-butylphenyl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.85),
(2*S*,3*R*)-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. 86),
(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. 87),
(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.88),
(2R,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.89).

In yet another embodiment, the present invention relates to the therapeutically effective dose of a compound of Formula I in combination with one or more of other therapeutic agents used for treating various inflammatory and allergic diseases. Examples of such therapeutic agents include, but not limited to,

1) Anti-inflammatory agents, experimental or commercial (i) such as nonsteroidal anti-inflammatory agents piroxicam, diclofenac, propionic acids, fenamates, pyrazolones, salicylates, PDE-4/p38 MAP Kinase/Cathepsin inhibitors (ii)leukotrienes LTC4/LTD4/LTE4/LTB4- Inhibitors, 5-lipoxygenase inhibitors and PAF- receptor antagonists, (iii) Cox-2 inhibitors (iv)MMP inhibitors,(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 selected from the group consisting of cyclosporine, azathioprine and methotrexate, anti-inflammatory corticosteroids.

The following definitions apply to terms as used herein

The term *"alkyl"* unless and otherwise specified refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. Groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, n-hexyl, n-decyl, tetradecyl, and the like exemplify this term.

It may further be substituted with one or more substituents selected from the groups consisting of alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, cycloalkyloxy, heterocyclyloxy, azido, cyano, halogen, hydroxy, thiol, aryloxy, heteroaryloxy, amino, aminosulfonyl, -COOH, -$COOR_4$, -NR_4R_5, -CHO, -$C(=Y)NR_4R_5$, -$OC(=O)NR_4R_5$, -$NHC(=Y)R_4$, -$NHC(=Y)NR_5R_x$, -$NHC(=O)OR_4$, –$NHSO_2R_4$; (wherein Y, R_4, R_5 and R_x are the same as defined earlier), nitro, -$S(O)_mR_4$ (wherein m is an integer from 0-2 and R_4 is the same as defined earlier). Unless otherwise constrained, all substituents may be further substituted by 1-3 substituents chosen from alkyl, -COOH, -$COOR_4$, -NR_4R_5, -$C(=Y)NR_4R_5$, -$OC(=O)NR_4R_5$, -$NHC(=Y)R_4$, hydroxy, alkoxy, halogen, CF_3, cyano and –$S(O)_mR_4$.

Alkyl group as defined above may also be interrupted by 1-5 atoms or groups independently chosen from oxygen, sulfur and -NR_a- (where R_a is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, acyl, aralkyl, -COOH, -COOR4, -SO_2R_4, -$C(=Y)NR_4R_5$)

The term *"alkenyl"* unless and otherwise specified refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 20 carbon atoms with *cis* or *trans* geometry. In the event that alkenyl is attached to the heteroatom, the double bond cannot be alpha to the heteroatom.

It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkynyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, cycloalkyloxy, heterocyclyloxy,

heteroaryloxy, azido, cyano, halogen, hydroxy, thiol, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, amino, aminosulfonyl, alkoxyamino, nitro, -COOH, $-COOR_4$, $-NR_4R_5$, $-C(=O)NR_4R_5$, $-OC(=O)NR_4R_5$, $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$; (wherein Y, R_4, R_5 and R_x are the same as defined earlier), $-S(O)_mR_4$ (wherein m is an integer from 0-2 and R_4 is the same as defined earlier). Unless otherwise constrained, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, -COOH, $-COOR_4$, hydroxy, alkoxy, halogen, $-CF_3$, cyano, $-NR_4R_5$, $-C(=Y)NR_4R_5$, $-OC(=O)NR_4R_5$, $-NHC(=Y)R_4$, and $-S(O)_mR_4$.

The term *"alkynyl"* unless and otherwise specified refers to a monoradical of an unsaturated hydrocarbon, preferably having from 2 to 20 carbon atoms.

In the event that alkynyl is attached to the heteroatom, the triple bond cannot be alpha to the heteroatom.

It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, azido, cyano, halogen, hydroxy, thiol, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, aryl, aralkyl, aryloxy, amino, aminosulfonyl, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, -COOH, $-COOR_4$, $-NR_4R_5$, $-C(=Y)NR_4R_5$, $-OC(=O)NR_4R_5$, $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$; (wherein Y, R_4, R_5 and R_x are the same as defined earlier), $-S(O)_mR_4$ (wherein R_4 and m are the same as defined earlier). Unless otherwise constrained, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, -COOH, $-COOR_4$, hydroxy, alkoxy, halogen, $-CF_3$, cyano, $-NR_4R_5$, $-C(=O)NR_4R_5$, $-OC(=O)NR_4R_5$, $-NHC(=Y)R_4$ and $-S(O)_mR_4$.

The term *"cycloalkyl"* refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a monocyclic ring or polycyclic (fused, spiro or bridged) rings, which may optionally contain one or more olefinic bonds, unless or otherwise constrained. Such cycloalkyl groups include, by way of example, monocyclic structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like, or polycyclic ring structures such as, tricyclo[3.3.1.1]decane, bicyclo[2.2.2]octane, bicyclo[4.4.0]decane, bicylco[4.3.0]nonane, bicyclo[3.3.0]octane, bicyclo [2.2.1] heptane and the like, or cyclic alkyl groups to which is fused an aryl group, for example indane, and the like.

It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, heteroaryloxy, heterocyclyloxy, azido, cyano, halogen, hydroxy, thiol, aryl, aralkyl, aryloxy, amino, aminosulfonyl, nitro, oxo, -CHO, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, -COOH, $-COOR_4$, $-NR_4R_5$, $-C(=Y)NR_4R_5$, $-OC(=O)NR_4R_5$, $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$; (wherein R_4, R_5 and R_x are the same as defined earlier), $-S(O)_mR_4$

(wherein R_4 and m are the same as defined earlier). Unless otherwise constrained, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, hydroxy, alkoxy, halogen, CF_3, cyano, $-NR_4R_5$, $-C(=O)NR_4R_5$, $-OC(=O)NR_4R_5$, $-NHC(=Y)R_4$ and $-S(O)_mR_4$.

The term *"aralkyl"* refers to aryl linked through alkyl portion and the said alkyl portion contains carbon atoms from 1-6 and aryl is the same as defined below.

The examples of aralkyl groups include but are not limited to are benzyl and the like.

The term *"aryl"* herein refers to a carbocyclic aromatic group for example, phenyl, naphthyl or anthryl ring and the like optionally substituted with 1 to 3 substituents selected from the group consisting of halogen (F, Cl, Br, I), hydroxy, -COOH, $-COOR_4$ (wherein R_4 is the same as defined earlier), alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heterocyclyloxy, heteroaryloxy, cycloalkyloxy, acyl, thioacyl, oxo, cyano, nitro, amino, -CHO, $-OCF_3$, $-CF_3$, $-SCF_3$, $-NR_4R_5$, $-C(=Y)NR_4R_5$, $-NHC(=Y)R_4$,- $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$, $(SO)_mR_4$ (wherein R_4, R_5, R_x, Y and m are the same as defined earlier), aryl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl. The said aryl group may optionally be fused with cycloalkyl group, heteroaryl group or heterocyclyl group.

The term *"aryloxy"* denotes the group O-aryl wherein aryl is the same as defined above.

The term *"heteroaryl"* unless and otherwise specified refers to an aromatic monocyclic or polycyclic (fused, spiro or bridged) ring system containing 1-8 heteroatom(s) independently selected from the group consisting of N, O and S. The said heteroaryl ring is optionally substituted with 1 to 3 substituent(s) selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, aryloxy, cycloalkyloxy, amino, acyl, thioacyl, oxo, -CHO, $-OCF_3$, $-CF_3$, $-SCF_3$, -COOH, $-COOR_4$ (wherein R_4 is the same as defined earlier), aryl, alkoxy, aralkyl, cyano, nitro, - NR_4R_5, $-C(=Y)NR_4R_5$, $-NHC(=Y)R_4$,- $NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, , $-NHSO_2R_4$, $S(O)_mR_4$ (wherein R_4, R_5, R_x, Y and m are the same as defined earlier). Unless otherwise constrained, the substituents are attached to the ring atom, be it carbon or heteroatom.

Examples of heteroaryl groups includes but are not limited to are pyridinyl, pyridazinyl, pyrazolyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, carbazolyl, isobenzofuranyl, thianthrene, isoxazolyl, triazinyl, tetrazolyl, furanyl, benzofuranyl, indolyl, isoindolyl benzothiazolyl, benzoxazolyl, imidazolyl, tetrazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazinonyl, benzothiazinonyl, benzotriazinyl and the like.

The term *"heterocyclyl"* unless and otherwise specified refers to nonaromatic monocyclic or polycyclic ring (fused, spiro or bridged) system having 1 to 8 heteroatoms selected from the group consisting of O, S and N. For heterocycles containing sulphur, the oxidized sulphur

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heterocycles containing SO or SO_2 are also included. The said heterocyclyl ring system is optionally benzofused or fused with heteroaryl and/or are optionally substituted wherein the substituents are selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, thioacyl, aryl, alkoxy, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, aryloxy, amino, cyano, nitro, oxo, -CHO, $-OCF_3$, $-CF_3$, $-SCF_3$, -COOH, $-COOR_4$, $-NR_4R_5$, $-C(=Y)NR_4R_5$, $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$, $(SO)_mR_4$ (wherein R_4, R_5, Rx, Y and m are the same as defined earlier). Unless or otherwise constrained, the substituents are attached to the ring atom, be it carbon or heteroatom. Also, unless or otherwise constrained the said heterocyclyl ring may optionally contain one or more olefinic bond(s).

Examples of heterocyclyl groups includes but are not limited to are tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydrobenzofuryl, azabicyclohexyl, dihydroindolyl, piperidinyl, isoxazolinyl, thiazolinyl, thiazolidinonyl, oxazolinyl or oxazolidinonyl.

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

The term *"Heteroarylalkyl"* refers to heteroaryl group linked through alkyl portion, wherein the alkyl having 1 to 6 carbon atoms and heteroaryl are the same as defined earlier.

The term *"Heterocyclylalkyl"* refers to heterocyclyl group linked through alkyl portion, wherein the alkyl having 1 to 6 carbon atoms and heterocyclyl are the same as defined earlier.

The term *"amino"* refers to $-NH_2$

The term *"acyl"* refers to $-C(=O)R_4$ wherein R_4 is the same as defined earlier.

The term *"thioacyl"* refers to $-C(=S)R_4$ wherein R_4 is the same as defined above;

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

The term *"leaving group"* generally refers to groups that exhibit the desirable properties of being labile under the defined synthetic conditions and also, being easily separated from synthetic products under defined conditions. Examples of such leaving groups includes but not limited to hal (Cl, Br, I), triflate, tosylate, 4-bromophenylsulfonate, 4-nitrophenylsulfonate, mesylate and the like.

The term "*Protecting groups*" is used herein to refer to known moieties which have the desirable property of preventing specific chemical reaction at a site on the molecule undergoing chemical modification intended to be left unaffected by the particular chemical modification. Also the term protecting group, unless or other specified may be used with groups such as hydroxy, amino, carboxyl and examples of such groups are found in T.W. Greene and P.G.M. Wuts, "Protective groups in organic synthesis", 3rd 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 group employed is not so critical so long as the derivatised moieties/moiety is/are stable to conditions of subsequent reactions and can be removed at the appropriate point without disrupting the remainder of the molecule.

The compounds of this invention contain one or more asymmetric carbon atoms and thus occur as diastereomers. These compounds also exist as conformers/rotamers. All such isomeric forms of these compounds are included in the present invention. Each stereogenic carbon may be of the *R* or *S* configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are envisioned as part of the invention.

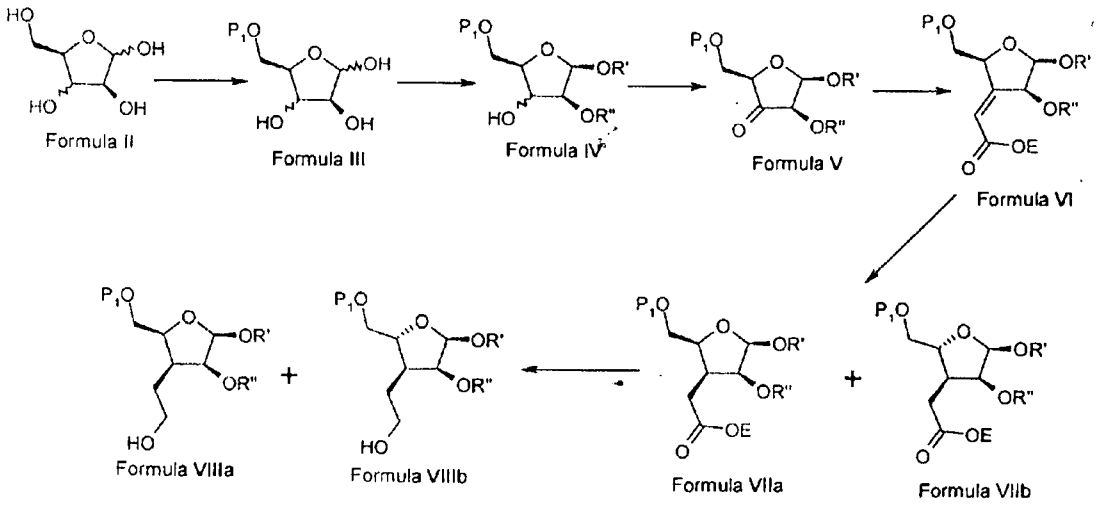
The term *"pharmaceutically acceptable salts"* forming part of this invention includes the salts of carboxylic acid moiety, which may be prepared by reacting the compound with appropriate base to provide corresponding base addition salts. Examples of such bases are alkali metal hydroxide including potassium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

The salt forms differ from the compound described herein in certain physical properties such as solubility, but the salts are otherwise equivalent for the purpose of this invention.

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 processes described herein may enable the synthesis of the compounds of the present invention. However, these may not be the only means by which the compounds described in the invention may be synthesized. Further, the various synthetic steps described herein may be performed in alternate sequences in order to furnish the desired compounds.

Scheme-I



Compounds of Formulae VIIIa and VIIIb can be prepared by following the synthetic route as depicted in Scheme I. Thus, a compound of Formula II is converted to a compound of Formula III (wherein P_1 is a silyl protecting group for example, tert-butyldimethylsilane, tert-butyldiphenylsilane or triisopropylsilane), which is then converted to a compound of Formula IV (wherein P_1 is defined as above, R' and R" together form an acetal protecting group). The compound of Formula IV is oxidized to form a compound of Formula V (wherein P_1, R' and R'' are same as defined above). The compound of Formula V is then converted to a compound of Formula VI (wherein P_1, R' and R" are same as defined above and E is alkyl group such as methyl, ethyl), which is then hydrogenated to form compounds of Formulae VIIa and VIIb (wherein P_1, R', R" and E are same as defined above). Compounds of Formulae VIIa and VIIb are reduced to form compounds of Formulae VIIIa and VIIIb (wherein P_1, R' and R'' are same as defined carlier).

Silylation of a compound of Formula II to form a compound of Formula III can be carried with silylating reagents such as tert-butyldimethylchlorosilane, triphenylchlorosilane, t-butyldiphenylchlorosilane in presence of a base, for example, imidazole or triethylamine in an organic solvent for example, dimethyl formamide, dimethylsulphoxide or acetonitrile.

Acetonation of a compound of Formula III to form a compound of Formula IV can be carried with acetone in excess as solvent in presence of mild acid catalyst for example, anhydrous copper (II) sulphate and camphorsulphonic acid, anhydrous zinc chloride and small amount of phosphoric acid, or anhydrous ferric chloride. Alternately, one may utilize trans-acetonation with dimethoxypropane in the presence of acid catalysts such as p-toluenesulfonic acid, sulfuric acid or montmorillonite-K.

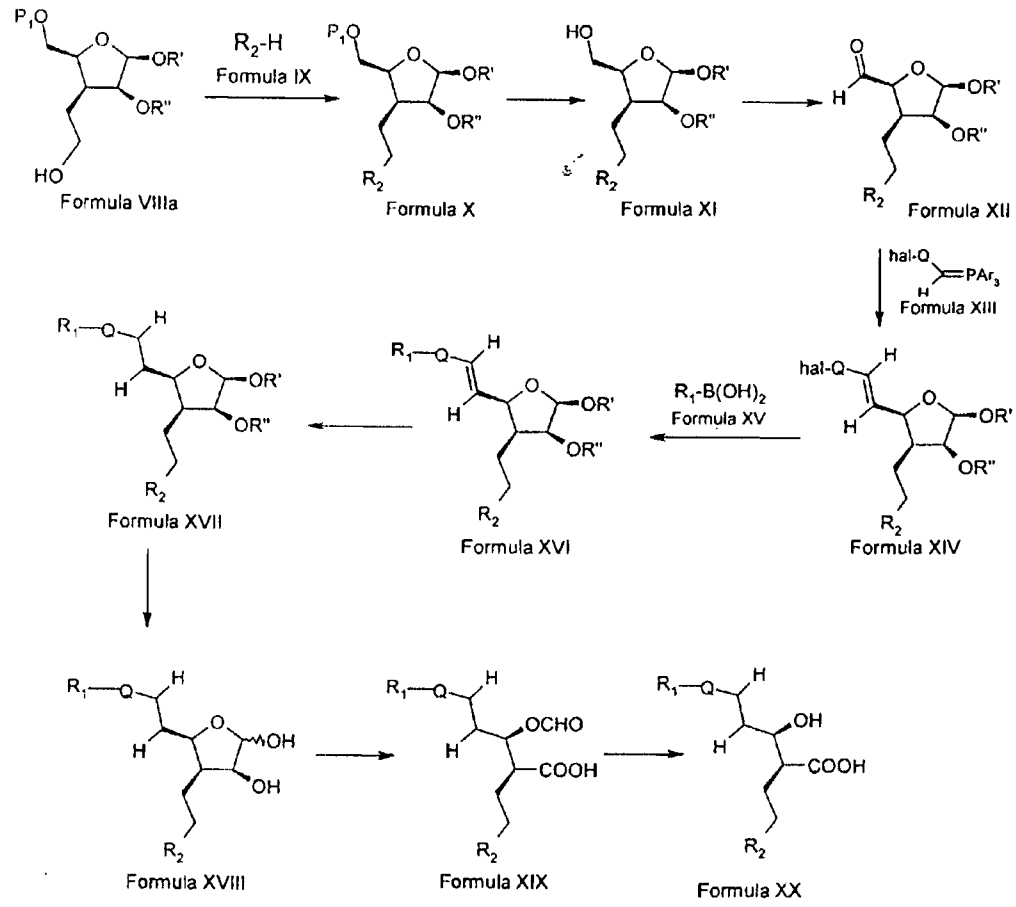
The compound of Formula IV can be oxidized to form a compound of Formula V using Swern oxidation (Dimethylsulphoxide and oxalyl chloride) or Corey-Kim oxidation (N-chlorosuccinimide and Dimethylsulphide) in presence of a base for example, triethylamine, diisopropylethylamine in a solvent for example, dichloromethane or toluene. Alternatively, the compound of Formula IV can be oxidized to a compound of Formula V in dichloromethane or chloroform with oxidizing agent such as Dess-Martin reagent, pyridinium chlorochromate (PCC) or pyridinium dichromate (PDC).

The compound of Formula V can be converted to a compound of Formula VI via Horner-Wadsworth-Emmons reaction, thus a compound of Formula V can be reacted with phosphophonate carbanions (produced in situ by treating trimethylphosphonoacetate or triethylphosphonoacetate with a base for example sodium hydride, potassium hydride, potassium tert-butoxide, sodium tert-butoxide, potassium carbonate, triethylamine in an organic solvents for example, tetrahydrofuran or dimethoxyethane) to give a compound of Formula VI. Alternately, the Wittig reaction can be carried out using the preformed Wittig reagent such as (carbethoxymethylene)-triphenylphosphorane.

Hydrogenation of a compound of Formula VI to form compounds of Formulae VIIa and VIIb can be carried with palladium on carbon in presence of hydrogen, in a suitable solvent for example methanol, ethanol, propanol, tetrahydrofuran, ethyl acetate or mixture of solvent for example, tetrahydrofuran and methanol.

Compounds of Formulae VIIa and VIIb can be reduced to give compounds of Formula VIIIa and VIIIb in the presence of reducing agent for example, lithium aluminium hydride, lithium triethyl borohydride or sodium borohydride in presence of a additive for example lithium chloride or aluminium chloride in an organic solvent for example tetrahydrofuran, diethylether or diglyme.

Scheme-II



Compounds of Formula XX can be prepared by following the synthetic route as depicted in Scheme II. Thus, a compound of Formula VIIIa (wherein P_1, R' and R'' are same as defined earlier), reacts with a compound of Formula IX (wherein R_2 is the same as defined earlier) to give a compound of Formula X (wherein P_1, R', R" and R_2 are same as defined earlier). The compound of Formula X undergo deprotection to form a compound of Formula XI (wherein R', R"and R_2 are same as defined earlier) which on oxidation gives a compounds of Formula XII (wherein R', R"and R_2 are same as defined earlier). The compound of Formula XII on reaction with a compound of Formula XIII (wherein Q is same as defined earlier, hal is Cl, Br or I and Ar is phenyl) forms a compound of Formula XIV (wherein Q, hal, R', R"and R_2 are same as defined earlier). The compound of Formula XIV then reacts with a compound of Formula XV (wherein R_1 is same as defined earlier) to form a compound of Formula XVI (wherein Q, R', R'', R_1 and R_2 are same as defined earlier) which is then hydrogenated to form a compound of Formula XVII (wherein Q, R', R'', $R_1$and R_2 are same as defined earlier). The compound of Formula XVII undergo deprotection to form a compound of Formula XVIII (wherein Q, $R_1$and

R_2 are same as defined earlier) which is then oxidatively cleaved to form a compound of Formula XIX (wherein Q, $R_1$and R_2 are same as defined earlier). The compound of Formula XIX is deformylated to form a compound of Formula XX (wherein Q, $R_1$and R_2 are same as defined earlier).

The reaction of a compound of Formula VIIIa with a compound of Formula IX to give a compound of Formula X can be carried out using triphenylphosphine or tributylphosphine and diethyl azodicarboxylate, diisoproyl azodicarboxylate or 1,1'-azodicarbonyldipiperidine in an organic solvent for example, tetrahydrofuran, dimethylformamide or toluene.

The compound of Formula X (when P_1 is t-butyldiphenylsilyl group) can be deprotected to form a compound of Formula XI with deprotecting agents for example, tetrabutylammonium fluoride or potassium fluoride in an organic solvent for example, tetrahydrofuran, dimethylformamide, diethyl ether or dioxane, optionally in the presence of crown ethers such as 18-crown-6. The oxidation of a compound of Formula XI to give a compound of Formula XII can be carried out similarly as that of conversion of a compound of Formula IV to form a compound of Formula V.

The compound of Formula XII can be converted to a compound of Formula XIV by reacting with a compound of Formula XIII (Wittig reagent i.e ylide (prepared by reacting a phosphonium salt (in turn prepared from triphenylphophine and alkyl halide) in a solvent for example, tetrahydrofuran, dimethyl sulphoxide or diethyl ether, with a strong base, for example, n-butyllithium, sodium hydride or potassium tert-butoxide).

The reaction of a compound of Formula XIV with a compound of Formula XV can be carried out in the presence of a metal catalyst, for example, 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 for example, potassium carbonate or cesium carbonate, in an organic solvent, for example, toluene, dimethyl sulphoxide, dimethylformamide, tetrahydrofuran, dioxane or diethyl ether.

Hydrogenation of a compound of Formula XVI to form a compound of Formula XVII can be carried out similarly as conversion of a compound of Formula VI to compounds of Formulae VIIa and VIIb.

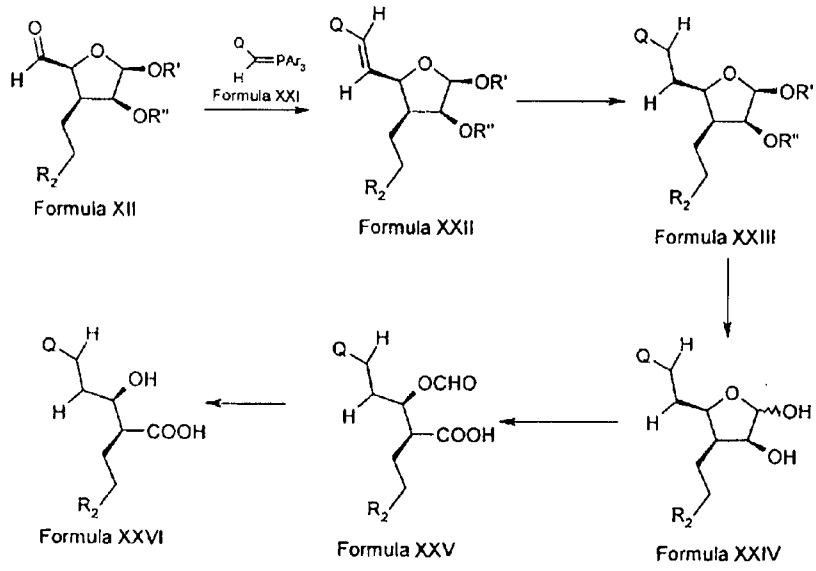
The compound of Formula XVII can be deprotected to form a compound of Formula XVIII with perchloric acid, acetic acid or hydrochloric acid in a mixture of solvent, for example, acetonitrile and water or solvent for example, tetrahydrofuran.

Conversion of a compound of Formula XVIII to form a compound of Formula XIX can be carried out by diol cleavage in presence of sodium metaperiodate, lead tetraacetate, pyridinium chlorochromate or manganese dioxide, in a co-solvents for example, tert-butanol-

water, methanol-tetrahydrofuran or tert-butanol-tetrahydrofuran followed by oxidation with potassium permangnate or with a mixture of sodium dihydrogen phosphate, sodium chlorite and hydrogen peroxide.

The compound of Formula XIX can be deformylated to form a compound of Formula XX in presence of a base for example, potassium carbonate, sodium carbonate or triethylamine in a solvent for example methanol or mixture of solvents for example, methanol and tetrahydrofuran.

Scheme-III



Compounds of Formula XXVI can be prepared by following the synthetic route as depicted in Scheme III. Thus, a compound of Formula XII reacts with a compound of Formula XXI (wherein Q is same as defined earlier and Ar is phenyl) to form a compound of Formula XXII (wherein Q, R', R'' and R_2 are same as defined earlier), which is further hydrogenated to form a compound of Formula XXIII (wherein Q, R', R''and R_2 are same as defined earlier). The compound of Formula XXIII is deprotected to form a compound of Formula XXIV (wherein Q and R_2 are same as defined earlier), which is then oxidatively cleaved to give a compound of Formula XXV(wherein Q and R_2 are same as defined earlier). The compound of Formula XXV is then converted to form a compound of Formula XXVI (wherein Q and R_2 are same as defined earlier).

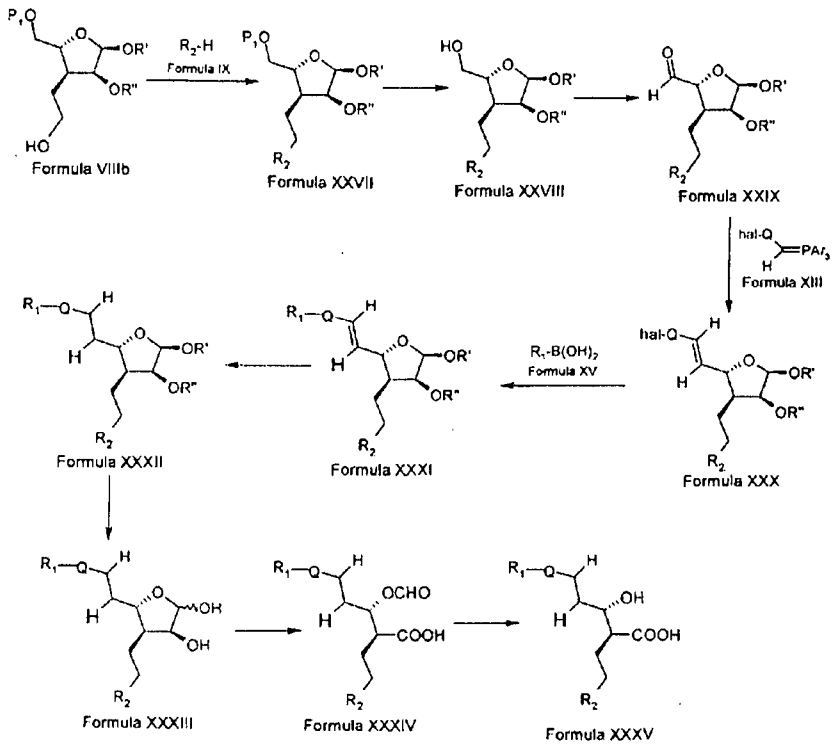
The reaction of a compound of Formula XII with a compound of Formula XXI to form a compound of Formula XXII can be carried out similarly as conversion of a compound of

Formula XII to a compound of Formula XIV. Hydrogenation of a compound of Formula XXII to give a compound of Formula XXIII can be carried out under similar conditions as that of conversion of a compound of Formula VI to compounds of Formulae VIIa and VIIb.

Deprotection of a compound of Formula XXIII to give a compound of Formula XXIV can be carried out similarly as conversion of a compound of Formula XVII to a compound of Formula XVIII. The oxidative cleavage of a compound of Formula XXIV to form a compound of Formula XXV can be carried out under similar condition as that of conversion of a compound of Formula XVIII to a compound of Formula XIX.

Deformylation of a compound of Formula XXV to form a compound of Formula XXVI can be carried out similarly as conversion of a compound of Formula XIX to give a compound of Formula XX.

Scheme-IV



Compounds of Formula XXXV can be prepared by following the synthetic route as depicted in Scheme IV. Thus, a compound of Formula VIIIb (wherein P_1, R' and R'' are same as defined earlier), reacts with a compound of Formula IX (wherein R_2 is the same as defined earlier) to give a compound of Formula XXVII (wherein P_1, R', R'' and R_2 are same as defined earlier). The compound of Formula XXVII is deprotected to form a compound of Formula XXVIII (wherein R', R'' and R_2 are same as defined earlier), which on oxidation gives a compound of

Formula XXIX (wherein R', R'' and R_2 are same as defined earlier). The compound of Formula XXIX on reaction with a compound of Formula XIII (wherein Q, hal and Ar are same as defined earlier) forms a compound of Formula XXX (wherein Q, hal, R', R''and R_2 are same as defined earlier) which then reacts with a compound of Formula XV (wherein R_1 is same as defined earlier) to form a compound of Formula XXXI (wherein Q, R', R'', R_1 and R_2 are same as defined earlier). The compound of Formula XXXI is then hydrogenated to form a compound of Formula XXXII (wherein Q, R', R'', $R_1$and R_2 are same as defined earlier) which then undergo deprotection to form a compound of Formula XXXIII (wherein Q, $R_1$and R_2 are same as defined earlier). The compound of Formula XXXIII is oxidatively cleaved to form a compound of Formula XXXIV (wherein Q, $R_1$and R_2 are same as defined earlier). The compound of Formula XXXIV is then converted to form a compound of Formula XXXV (wherein Q, $R_1$and R_2 are same as defined earlier).

The reaction of a compound of Formula VIIIb with a compound of Formula IX to give a compound of Formula XXVII can be carried out similarly as that of conversion of a compound of Formula VIIIa to form a compound of Formula X.

Deprotection of a compound of Formula XXVII to give a compound of Formula XXVIII can be carried out similarly as that of deprotection of a compound of Formula X to form a compound of Formula XI.

Oxidation of a compound of Formula XXVIII to give a compound of Formula XXIX can be carried out similarly as that of conversion of a compound of Formula IV to form a compound of Formula V.

The reaction of a compound of Formula XXIX with a compound of Formula XIII to form a compound of Formula XXX can be carried out under similar condition as that of conversion of a compound of Formula XII to form a compound of Formula XIV.

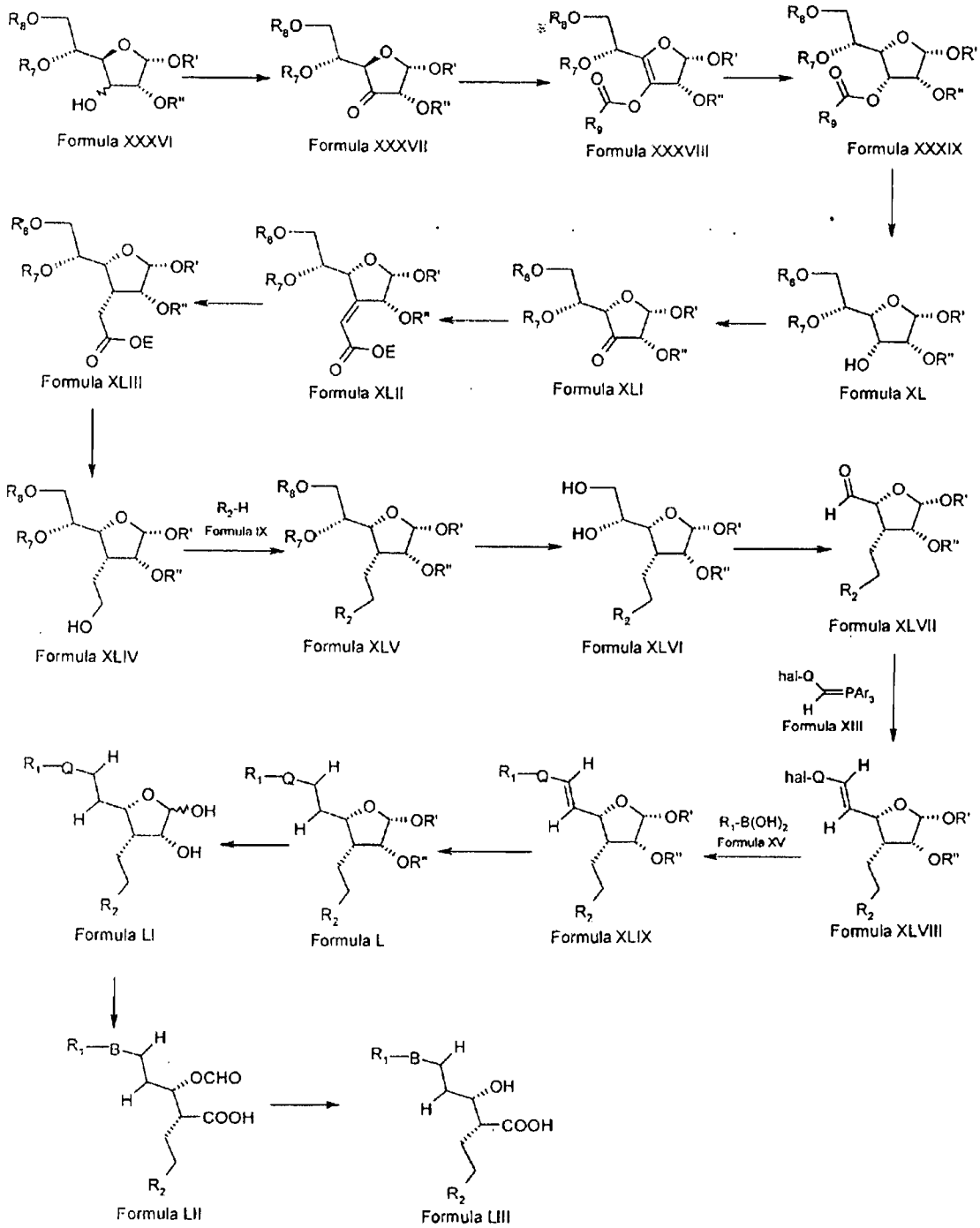
Coupling of a compound of Formula XXX with a compound of Formula XV to form a compound of Formula XXXI can be carried out similarly as conversion of a compound of Formula XIV to form a compound of Formula XVI.

Hydrogenation of a compound of Formula XXXI to form a compound of Formula XXXII can be carried out similarly as conversion of a compound of Formula VI to form compound of Formulae VIIa and VIIb. The compound of Formula XXXII can be deprotected to form a compound of Formula XXXIII under similar condition as that of conversion of a compound of Formula XVII to form a compound of Formula XVIII.

Oxidative cleavage of a compound of Formula XXXIII to form a compound of Formula XXXIV can be carried out similarly as conversion of a compound of Formula XVIII to give a compound of Formula XIX.

Conversion of a compound of Formula XXXIV to form a compound of Formula XXXV can be carried out under similar condition as that of conversion of a compound of Formula XIX to form a compound of Formula XX.

Scheme-V



Compounds of Formula LIII can be prepared by following the synthetic route as depicted in Scheme V. Thus, a compound of Formula XXXVI (wherein R_7 and R_8 together form a acetal

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protecting group, R' and R" are same as described earlier) is oxidized to form a compound of Formula XXXVII (wherein R_7, R_8, R' and R" are same as described earlier) which is then converted to form a compound of Formula XXXVIII (wherein R_7, R_8, R' and R" are same as described earlier, R_9 is alkyl or aryl). The compound of Formula XXXVIII is hydrogenated to give a compound of Formula XXXIX (wherein R_7, R_8, R' and R" are same as described earlier, R_9 is alkyl or aryl) which is then hydrolyzed to give a compound of Formula XL (wherein R_7, R_8, R' and R" are same as described earlier).The compound of Formula XL is oxidized to give a compound of Formula XLI which is then converted to form a compound of Formula XLII (wherein R_7, R_8, R',R" and E are same as described earlier). The compound of Formula XLII is hydrogenated to form a compound of Formula XLIII (wherein R_7, R_8, R',R" and E are same as described earlier) which is then reduced to form a compound of Formula XLIV (wherein R_7, R_8, R', and R"are same as described earlier).The compound of Formula XLIV is then reacted with a compound of Formula IX (wherein R_2 is defined earlier) to afford a compound of Formula XLV(wherein R_7, R_8, R', R" and R_2 are same as described earlier) which is then deprotected to form a compound of Formula XLVI (wherein R', R" and R_2 are same as described earlier). The compound of Formula XLVI is oxidized to form a compound of Formula XLVII (wherein R', R" and R_2 are same as described earlier) which then reacts with a compound of Formula XIII (wherein Q, hal and Ar are same as defined earlier) to form a compound of Formula XLVIII (wherein Q, hal, R', R''and R_2 are same as defined earlier). The compound of Formula XLVIII is then reacted with a compound of Formula XV (wherein R_1 is same as defined earlier) to give a compound of Formula XLIX (wherein Q, R', R'', R_1 and R_2 are same as defined earlier) which is then hydrogenated to form a compound of Formula L (wherein Q, R', R'' , $R_1$and R_2 are same as defined earlier). The compound of Formula L is deprotected to form a compound of Formula LI (wherein Q, $R_1$and R_2 are same as defined earlier) which is then oxidatively cleaved to form a compound of Formula LII (wherein Q, $R_1$and R_2 are same as defined earlier). The compound of Formula LII is then converted to form a compound of Formula LIII (wherein Q, $R_1$and R_2 are same as defined earlier).

Oxidation of a compound of Formula XXXVI to form a compound of Formula XXXVII can be carried out under similar condition as that of oxidation of a compound of Formula IV to form a compound of Formula V. The compound of Formula XXXVII can be converted to a compound of Formula XXXVIII in presence of acetic anhydride or benzoic anhydride in presence of base such as pyridine, triethylamine or morpholine as described in *Can. J. Chem 1969, 47, 3989.*

The compound of Formula XXXVIII can be hydrogenated to form a compound of Formula XXXIX similarly as that of hydrogenation of a compound of Formula VI to give compounds of Formulae VIIa and VIIb. The hydrolysis of a compound of Formula XXXIX to form a

compound of Formula XL can be carried out with a base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate in presence of a solvent for example, methanol, ethanol or isopropanol. The compound of Formula XL can be oxidized to form a compound of Formula XLI similarly as that of conversion of a compound of Formula IV to form a compound of Formula V.

Conversion of a compound of Formula XLI to form a compound of Formula XLII can be carried out under similar condition as that of conversion of a compound of Formula V to form a compound of Formula VI. The compound of Formula XLII can be hydrogenated to form a compound of Formula XLIII similarly as that of conversion of compound of Formula VI to compounds of Formulae VIIa and VIIb. The reduction of a compound of Formula XLIII to form a compound of Formula XLIV can be carried out under similar condition as that of reduction of compounds of Formulae VIIa and VIIb to form compounds of Formulae VIIIa and VIIIb. The reaction of a compound of Formula XLIV with a compound of Formula IX to form compound of Formula XLV can be carried out similarly as that of conversion of a compound of Formula VIIIa to form a compound of Formula X.

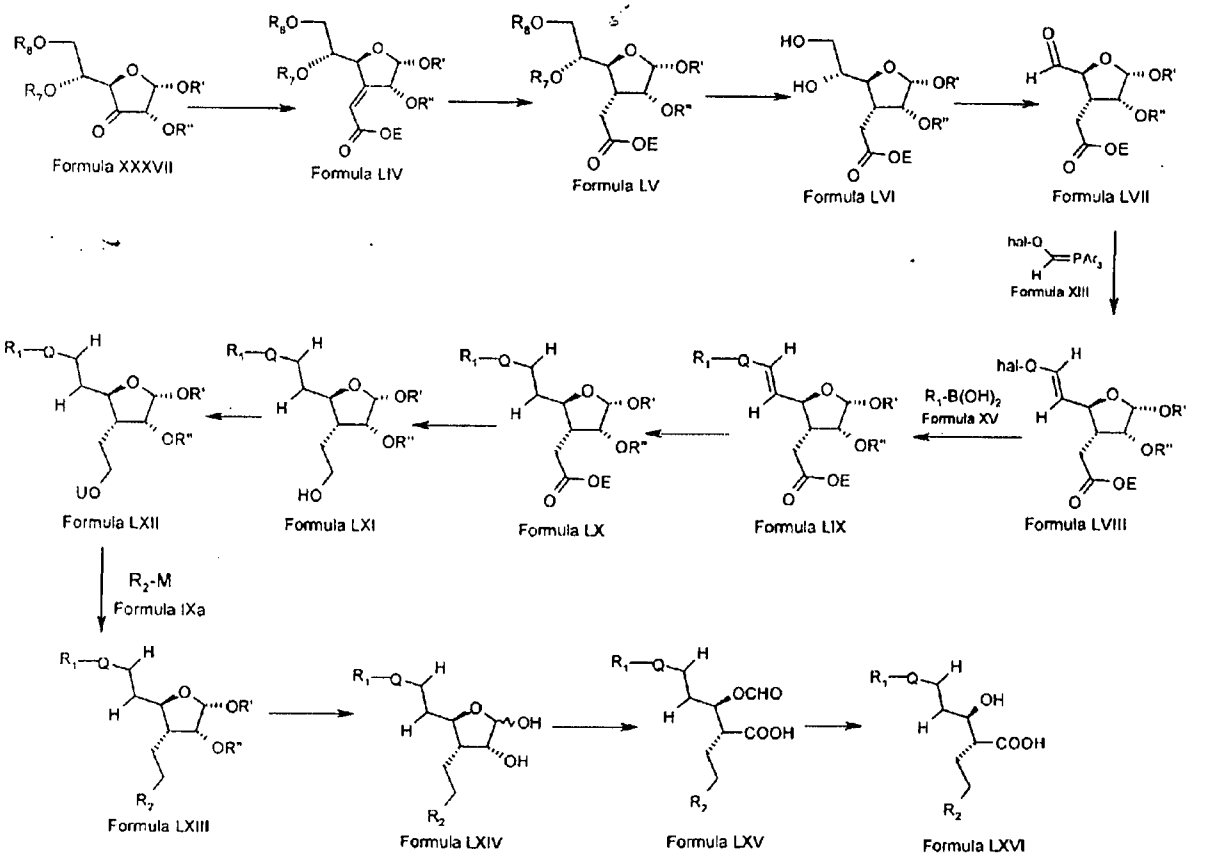
Selective acetonide deprotection of a compound of Formula XLV to form a compound of Formula XLVI can be carried out with perchloric acid in solvent for example, tetrahydrofuran or diethyl ether or trifluoroacetic acid in dichloromethane. Oxidation of a compound of Formula XLVI to form a compound of Formula XLVII can be carried out with sodium metaperiodate, lead tetraacetate, pyridinium chlorochromate or manganese dioxide in solvent for example, methanol, ethanol or tert-butanol .

The reaction of a compound of Formula XLVII with a compound of Formula XIII to form a compound of Formula XLVIII can be carried out similarly as that of conversion of compound of Formula XII to form a compound of Formula XIV. Coupling of a compound of Formula XLVIII with a compound of Formula XV to form a compound of Formula XLIX can be carried out similarly as conversion of a compound of Formula XIV to form a compound of Formula XVI. The compound of Formula XLIX can be hydrogenated to form a compound of Formula L under similar condition as that of conversion of compound of Formula VI to compound of Formulae VIIa and VIIb. Deprotection of a compound of Formula L to give a compound of Formula LI can be carried out under similar condition as that of conversion of a compound of Formula XVII to form a compound of Formula XVIII.

The oxidative cleavage of a compound of Formula LI to form a compound of Formula LII can be done similarly as that of conversion of a compound of Formula XVIII to form a compound of Formula XIX. The compound of Formula LII can be converted to a compound of Formula LIII

under similar condition as that of conversion of compound of Formula XIX to form compound of Formula XX.

Scheme-VI



Compounds of Formula LXVI can be prepared by following the synthetic route as depicted in Scheme VI. Thus, a compound of Formula XXXVII (wherein R_7, R_8, R' and R" same as described earlier) is converted to form a compound of Formula LIV (wherein R_7, R_8, R', R" and E are same as described earlier) which is then hydrogenated to form a compound of Formula LV (wherein R_7, R_8, R', R" and E are same as described earlier). The compound of Formula LV is selectively deprotected to form a compound of Formula LVI (wherein R', R" and E are same as described earlier) which on oxidation forms a compound of Formula LVII (wherein R', R" and E are same as described earlier). The compound of Formula LVII is reacted with a compound of Formula XIII (wherein Q, hal and Ar are same as defined earlier) to form a compound of Formula LVIII (wherein Q, hal, R', R''and E are same as defined earlier) which is then coupled with a compound of Formula XV (wherein R_1 is same as defined earlier) to give a compound of Formula LIX (wherein Q, R', R'', R_1 and E are same as defined earlier). The compound of

Formula LIX is hydrogenated to form a compound of Formula LX (wherein Q, R', R'', $R_1$and E are samc as defined earlier) which is then reduced to form a compound of Formula LXI (wherein R', R" and R_1 are same as described earlier). The compound of Formula LXI is activated to form a compound of Formula LXII (wherein R', R", R_1 are same as described earlier and U is O-activating group like mesyl, tosyl or triflate), which is then reacted with a compound of Formula IXa (wherein R_2 is defined earlier and M is metal for example, potassium, lithium or sodium) to form a compound of Formula LXIII (wherein R', R",Q, $R_1$and R_2 are same as defined earlier). The compound of Formula LXIII is then deprotected to form a compound of Formula LXIV (wherein Q, $R_1$and R_2 are same as defined earlier) which is oxidatively cleaved to form a compound of Formula LXV (wherein Q, $R_1$and R_2 are same as defined earlier).The compound of Formula LXV is deformylated to form a compound of Formula LXVI (wherein Q, $R_1$and R_2 are same as defined earlier).

The compound of Formula XXXVII can be converted to form a compound of Formula LIV under similar condition as that of conversion of a compound of Formula V to form a compound of Formula VI. Hydrogenation of a compound of Formula LIV to form a compound of Formula LV can be carried out similarly as that of conversion of a compound of Formula VI to form compounds of Formulae VIIa and VIIb.

The compound of Formula LV can be selectively deprotected to form a compound of Formula LVI under similar conditions as that of conversion of a compound of Formula XLV to give a compound of Formula XLVI. The compound of Formula LVI can be oxidized to form a compound of Formula LVII similarly as that of conversion of a compound of Formula XLVI to form a compound of Formula XLVII.

The reaction of a compound of Formula LVII with a compound of Formula XIII to form a compound of Formula LVIII can be carried out under similar conditions as that of conversion of compound of Formula XII to form a compound of Formula XIV. The compound of Formula LVIII can be coupled with a compound of Formula XV to give a compound of Formula LIX under similar condition as that of conversion of a compound of Formula XIV to form a compound of Formula XVI. Hydrogenation of a compound of Formula LIX to form a compound of Formula LX can be carried out under similar condition as that of conversion of a compound of Formula VI to form compounds of Formulae VIIa and VIIb.

The compound of Formula LX can be reduced to form a compound of Formula LXI under similar condition as that of conversion of compound of Formulae VIIa and VIIb to form compounds of Formulae VIIIa and VIIIb.

A compound of Formula LXI is activated to form a compound of Formula LXII in a solvent for example dichloromethane, toluene or dichloroethane using a base for example

triethylamine, diisopropylamine or N-methylmorpholine using suitable sulphonyl chloride for example methanesulphonyl chloride or p-toluene sulphonyl chloride. The reaction of a compound of Formula LXII with a compound of Formula IXa to yield a compound of Formula LXIII 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 LXII with a compound of Formula IX to yield a compound of Formula LXIII 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. Alternately, a compound of Formula LXI can be converted to a compound of Formula LXIII following similar protocols as that of the reaction of a compound of Formula VIIIa with a compound of Formula IX to give a compound of Formula X.

The compound of Formula LXIII can be deprotected to form a compound of Formula LXIV similarly as that of conversion of a compound of Formula XVII to form a compound of Formula XVIII.

The oxidative cleavage of a compound of Formula LXIV to give a compound of Formula LXV can be done similarly as that of conversion of a compound of Formula XVIII to form a compound of Formula XIX. The compound of Formula LXV can be deformylated to form a compound of Formula LXVI under similar condition as that of conversion of a compound of Formula XIX to form a compound of Formula XX.

Following compounds were prepared following the scheme I, II, III, IV, V or VI described above:

Compound Nos. 1 to 81, 86-88 were prepared following Scheme I and II.

Compound Nos. 82 to 85 were prepared following Scheme II and III.

Compound No 89, was prepared following Scheme VI.

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

Example set forth demonstrates the general synthetic procedure for the preparation of representative compounds. The examples are provided to illustrate particular aspect of the disclosure and should not be constrained to limit the scope of the present invention

EXPERIMENTAL

Synthesis of starting materials:

Synthesis of 6-methyl-1,2,3-benzotriazin-4(3*H*)-one

The title compound was prepared following the procedure outlined in *Journal of Medicinal Chemistry, 1992, 35(14), 2626-2630.*

The following analogues of 6-methyl-1,2,3-benzotriazin-4(3*H*)-one *were prepared similarly,*

8-methyl-1,2,3-benzotriazin-4(3H)-one

7-methyl-1,2,3-benzotriazin-4(3H)-one

8-methoxy-1,2,3-benzotriazin-4(3H)-one

7-chloro-1,2,3-benzotriazin-4(3H)-one

6,7-difluoro-1,2,3-benzotriazin-4(3H)-one

8-fluoro-1,2,3-benzotriazin-4(3H)-one

5-fluoro-1,2,3-benzotriazin-4(3H)-one

5-(6-methoxypyridin-3-yl)-1,2,3-benzotriazin-4(3H)-one

7-(6-methoxypyridin-3-yl)-1,2,3-benzotriazin-4(3H)-one

Synthesis of 5-tert-butyl-1H-isoindole-1,3(2H)-dione

The title compound was prepared following the procedure outlined in *Chem. Ber, 1877, 10, 1163.*

Mass (m/z): 204.12(M^+ +1)

The following analogues of 5-tert-butyl-1H-isoindole-1,3(2H)-dione *were prepared similarly,*

4-fluoro-1H-isoindole-1,3(2H)-dione

5-chloro-1H-isoindole-1,3(2H)-dione

Synthesis of (4-bromobenzyl)(triphenyl)phosphonium bromide

A mixture of 1-bromo-4-(bromomethyl)benzene (5g) and triphenylphosphine(5.24 g) in xylene (20 mL) were heated to reflux for 18 h. The reaction mixture was cooled, filtered, washed with hexane and tried under vacuum to afford the title compound (8 g).

Mass (m/z):433.9 (M^+ +1)

Following Wittig salts were prepared similarly.

[(4-bromo-2-thienyl)methyl]triphenyl phosphonium bromide

[(6-bromopyridin-3-yl)methyl](triphenyl)phosphonium bromide

(4-bromo-2-fluorobenzyl)(triphenyl)phosphonium bromide

4-tert-butylbenzyl)(triphenyl)phosphonium bromide

triphenyl[4-(trifluoromethyl)benzyl]phosphonium bromide

benzyl(triphenyl)phosphonium bromide

(4-bromo-3-fluorobenzyl)(triphenyl)phosphonium bromide

EXAMPLE-1

Synthesis of (2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4-pyrimidin-5-ylphenyl)pentanoic acid (Compound No.1)

Step a: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-D-arabinofuranose

D-Arabinose (200 g) and imidazole (199 g) were placed in a three-neck round bottom flask and connected to high vacuum for 30 min. The vacuum was released under nitrogen atmosphere and dimethylformamide (1.8 L) was added to the above mixture at room temperature followed by drop wise addition of t-butyldiphenylchlorosilane (443 mL) for 10 min under nitrogen atmosphere. The resulting mixture was stirred for 16 h at the same temperature. Dimethylformamide was evaporated under the reduced pressure. Residue was taken in ethyl acetate and washed with water. Organic layer was dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure to obtain a crude residue which was purified by column chromatography over silica gel using 80% ethyl acetate in hexane as eluant to afford the title compound (273 g).

Mass (m/z): 389.37(M^+ +1)

Step b: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-1,2-O-isopropylidene-β-D-arabinofuranose

To the solution of compound (273 g), obtain from step a above, in acetone (2.5 L) was charged DL-camphorsulphonic acid (16 g) and anhydrous copper sulphate (346 g) under the nitrogen atmosphere at room temperature. The reaction mixture was stirred for 16 h at the same temperature. Saturated solution of sodium bicarbonate (2 L) was added drop wise till basic pH was attained and reaction mixture was further stirred for 2 h at the same temperature. The resulting mixture was filtered using Buckner funnel and residue was washed with acetone. Filtrate was concentrated, dissolved in ethyl acetate and washed with water. Organic layer was dried over anhydrous sodium sulphate, filtered and evaporated under the reduced pressure to furnish the title compound (295 g).

Mass (m/z): 429.41(M^+ +1)

Step c: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-1,2-O-isopropylidene-β-D-threo-pentofuranos-3-ulose

Oxalyl chloride (145 ml) and dichloromethane (1 L) were taken in a three neck round bottom flask and cooled to -75^0 C under nitrogen atmosphere. Dimethylsulfoxide (212 mL) was added dropwise to the above solution maintaining the reaction temperature at -70^0 C. The reaction mixture was stirred for 30 min at the same temperature, then solution of 5-O-[tert-butyl(diphenyl)silyl]-1,2-O-isopropylidene-β-D-arabinofuranose (285 g) in dichloromethane (1 L) was added slowly to the above mixture maintaining the reaction temperature -70^0 C. After 20 min of the above addition, triethylamine (560 mL) was added drop wise at the same temperature. Saturated solution of ammonium chloride in water (1.5 L) was then added after 30 min and reaction temperature was allowed to rise up to room temperature. The reaction mixture was extracted with dichloromethane. Organic extracts were dried over anhydrous sodium sulphate, filtered and evaporated under the reduced pressure to afford the title compound (285 g)

Step d: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-ethoxy-2-oxoethylidene)-1,2-O-isopropylidene-β-D-threo-pentofuranose

To the suspension of sodium hydride (29.4 g, 60% in oil.) in tetrahydrofuran (1L) at 0^0 C was charged triethyl phosphonoacetate (200 ml).After 20 min, a solution compound (285 g), obtained from step c above, in tetrahydrofuran (2 L) was added drop wise and reaction mixture was stirred for 1 h at the same temperature. Saturated solution of ammonium chloride in water (1.5 L) was added to reaction mixture. The resulting mixture was extracted with ethyl acetate (2 x 2.5 L).Combined extracts were dried over anhydrous sodium sulphate and evaporated under the reduced pressure to yield a residue which was purified by column chromatography over silica gel using 15% ethyl acetate in hexane as eluant to afford the title compound (275 g).

Mass (m/z): 497.43 (M^+ +1)

Step e: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-ethoxy-2-oxoethyl)-1,2-O-isopropylidene-β-D-lyxofuranose and 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-ethoxy-2-oxoethyl)-1,2-O-isopropylidene-α-L-ribofuranose

10% Palladium on charcoal (100 g) was added to the solution of compound (275 g), obtained from step d above, in tetrahydrofuran (2 L) and methanol (1 L) at room temperature and hydrogen was supplied at the pressure of 50 psi (Paar apparatus).The reaction mixture was filtered through celite pad and the residue was washed with ethyl acetate (2.5 L). The filterate was concentrated to afford a mixture of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-ethoxy-2-oxoethyl)-1,2-O-isopropylidene-β-D-lyxofuranose and 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-ethoxy-2-oxoethyl)-1,2-O-isopropylidene-α-L-ribofuranose (275 g).

Mass (m/z): 499.42 (M^+ +1)

Step f: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-hydroxyethyl)-1,2-O-isopropylidene-β-D-lyxofuranose and 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-hydroxyethyl)-1,2-O-isopropylidene-α-L-ribofuranose

To the suspension of lithium aluminium hydride (48 g) in tetrahydrofuran (1 L) was added a solution of compound (275 g), obtained from step e above, in tetrahydrofuran (1.5 L) at -50^{0}C. The resulting mixture was allowed to attain the temperature 0^{0}C. The reaction mixture was stirred for 30 min at same temperature and again cooled to -50^{0}C. Ethyl acetate (2 L) was added slowly while maintaining the above mentioned temperature (-50^{0}C). Aqueous solution of ammonium chloride (100 g) in water (2.5 L) was added at the same temperature. Reaction mixture was slowly allowed to warm to the room temperature and reaction mixture was stirred for 12 h at same temperature. The reaction mixture was then filtered through celite pad and residue was washed with ethyl acetate (1 L). Organic layer was dried over anhydrous sodium sulphate, filtered, concentrated under reduced pressure and the residue thus obtained was purified by column chromatography over silica gel using 50% ethyl acetate in hexane as eluant to afford the 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-hydroxyethyl)-1,2-O-isopropylidene-β-D-lyxofuranose (130 g) and 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-hydroxyethyl)-1,2-O-isopropylidene-α-L-ribofuranose (40.0 g).

Mass (m/z): 457.39(M^+ +1).

Step g: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-1,2-O-isopropylidene-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-β-D-lyxofuranose

5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-hydroxyethyl)-1,2-O-isopropylidene-β-D-lyxofuranose (35g), triphenylphosphine (30.8g) and 1,2,3-benzotriazin-4(3*H*)-one (12.6g) were dried in high vacuum in a round bottom flask for 10 min. Then vacuum was released under nitrogen atmosphere and tetrahydrofuran (70mL) was added to the above reaction mixture. The reaction mixture was cooled to 0°C and diisopropyl azodicarboxylate (17mL) was added slowly. The reaction mixture was stirred for 30 min at same temperature, and then quenched with water and extracted with ethyl acetate. Organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated to obtain a residue which was purified by column chromatography over silica gel using 30% ethyl acetate in hexane as eluant to afford the title compound (50g).

Mass (m/z):586.05 (M^+ +1)

Step h: Synthesis of 3-deoxy-1,2-O-isopropylidene-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-β-D-lyxofuranose

To a solution of compound (50g), obtained from step g above, in dry tetrahydrofuran (400mL) at 0°C, was added tetra-butyl ammonium fluoride (170mL). The resulting mixture was initially

stirred at the 0°C for 1h and then at room temperature for 4h. The reaction mixture was cooled to 0°C, quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulphate and concentrated. The residue thus obtained was purified by column chromatography over silica gel using 80% ethyl acetate in hexane as eluant to furnish the title compound (22 g).

Mass (m/z):369.98 (M^+ +23)

Step i: Synthesis of (5S)-3-deoxy-4,5-O-isopropylidene-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-D-arabino-pentodialdo-5,2-furanose

Oxalyl chloride (13.7mL) and dichloromethane (300mL) were taken in a three neck round bottom flask and cooled to -78^{0}C. Dimethylsulfoxide (20.2mL) was added drop wise to the reaction mixture. The reaction mixture was warmed to -35°C for 5 to 10 min and again cooled to -78°C. 3-deoxy-1,2-O-isopropylidene-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-β-D-lyxo-furanose (22 g) in dichloromethane (200mL) was added slowly while maintaining the same temperature. The reaction mixture was stirred for 45 min till reaction temperature reached to -35°C. The reaction mixture was again cooled to -78°C and triethylamine (53mL) was added. The reaction mixture was stirred for additional 30 min and the temperature was allowed to reach to -35°C. Reaction mixture was quenched with saturated solution of ammonium chloride and extracted with dichloromethane. The combined organic layer was washed with water and brine solution, dried over anhydrous sodium sulphate and concentrated to furnish the title compound (22g).

Step j: Synthesis of 3-(2-{(3aS,5R,6S,6aS)-5-[(E)-2-(4-bromophenyl)vinyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one

To the suspension of sodium hydride (3.3g, 60% in oil) in tetrahydrofuran (50mL) cooled to 0^{0}C, was added (4-bromobenzyl)triphenylphosphonium bromide (48.8g) in tetrahydrofuran (100mL). (5S)-3-deoxy-4,5-O-isopropylidene-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-D-arabino-pentodialdo-5,2-furanose (22g) in tetrahydrofuran (100mL) was added drop wise after 20 min, and reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with water and extracted with ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure and the residue thus obtained was purified by column chromatography using 30% ethyl acetate in hexane as eluant to furnish the title compound (24.5g).

Mass (m/z):498.84 (M^+ +1)

Step k: Synthesis of 3-(2-{(3aS,5R,6S,6aS)-2,2-dimethyl-5-[(E)-2-(4-pyrimidin-5-ylphenyl)vinyl]tetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one

A mixture of compound (0.35g), obtained from step j above, pyrimidin-5-ylboronic acid (0.174g), tetrakistriphenylphosphinepalladium (0) (0.081g) and potassium carbonate (0.291g) was dried under high vacuum for 10 min and dry dimethylformamide (5mL) was added at room temperature. The reaction mixture was heated at 120°C for 2 h, and then quenched with water and extracted with ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 40% ethyl acetate in hexane as eluant to afford the title compound (0.3g).

Mass (m/z): 498.0(M^+ +1)

Step l: Synthesis of 3-(2-{(3aS,5R,6S,6aS)-2,2-dimethyl-5-[2-(4-pyrimidin-5-ylphenyl)ethyl]tetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one

To the solution of compound (0.3g), obtained from step k above, in a solvent mixture of tetrahydrofuran: methanol (10mL, 1:1) was added 10% Palladium on charcoal (0.15g) at room temperature and the reaction mixture was hydrogenated with hydrogen at the pressure of 35 psi for 4 h in Paar apparatus. The reaction mixture was filtered through celite pad and the residue was washed with methanol. The filtrate was concentrated to afford the title compound (0.3g).

Step m: Synthesis of 3-(2-{(2R,3R,4S,5R)-4,5-dihydroxy-2-[2-(4-pyrimidin-5-ylphenyl)ethyl]tetrahydrofuran-3-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one

Perchloric acid (0.2mL) was added to a solution of compound (0.3g), obtained from step l above, in acetonitrile (4mL) and water (0.2mL) at room temperature. The reaction mixture was heated to 55°C for 30 min. Reaction mixture was then quenched using sodium bicarbonate solution. The solvents were evaporated under reduced pressure. The residue thus obtained was taken in ethyl acetate and water. Organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was concentrated under the reduced pressure to yield the title compound (0.25g).

Step n: Synthesis of (2S,3R)-3-(formyloxy)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4-pyrimidin-5-ylphenyl)pentanoic acid

To a solution of 3-(2-{(2R,3R,4S,5R)-4,5-dihydroxy-2-[2-(4-pyrimidin-5-ylphenyl)ethyl]-tetrahydrofuran-3-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one (0.25g) in a tert-butanol: tetrahydrofuran (5mL:5mL) at 0°C was added a solution of sodium metaperiodate (0.465 g in 5 mL of water). The reaction mixture was stirred for 2 h at same temperature and potassium permangnate (0.017g) was added at 0°C. After stirring, the reaction mixture for additional 6h at room temperature, reaction mixture was evaporated on rota-evaporator the residue was taken into water and extracted with ethyl acetate. Organic layer was washed with water and brine

solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure, to afford the title compound (0.25g).

Step o: Synthesis of (2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4-pyrimidin-5-ylphenyl)pentanoic acid

Potassium carbonate (0.081g) was added to a solution of compound (0.25g), obtained from step n above, in methanol (5mL) and tetrahydrofuran (5mL) at 0°C. The reaction mixture was stirred at room temperature for 3h. Solvents were evaporated and the residue was taken into water and ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure obtain a residue which was purified by column chromatography over silica gel using 60% ethyl acetate in hexane as eluant to afford the title compound (0.030g).

Mass (m/z):446.0 (M^+ +1)

^{1}HNMR (CD_3OD): 9.09 (s, 1H), 9.03 (s, 1H), 8.30 (d, 1H, 8Hz), 8.14 (d, 1H, 8Hz), 8.05- 8.03 (m, 1H), 7.89-7.87 (m, 1H), 7.61 (d, 2H, 8Hz), 7.53- 7.59 (m,1H), 7.35 (d, 2H, 8Hz), 4.57- 4.52 (m, 2H), 3.79-3.77 (m, 1H), 2.89 -2.87 (m, 1H), 2.69 - 2.67 (m, 1H), 2.47- 2.46 (m, 1H), 2.29-2.25 (m, 2H), 1.82- 1.77 (m, 2H).

Following compounds were prepared similarly

(2S,3R)-2-[2-(5-tert-butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 2),
Mass (m/z): 531.09 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 3),
Mass (m/z): 458.82(M^+ +1)
(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. 4),
(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 5),
Mass (m/z): 479.70(M^+ +1)
(2S,3R)-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 6),
Mass (m/z):458.94 (M^+ +1)
(2S,3R)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 7),
Mass (m/z): 472.87 (M^+ +1)
(2S,3R)-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. 8),
(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 9),
Mass (m/z):461.87 (M^+ +1)
(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 10),
Mass (m/z):473.79 (M^+ +1)
(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 11),

Mass (m/z):493.81 (M^+ +1)
(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 12),
Mass (m/z): 479.77(M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 13),
Mass (m/z):473.86 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 14),
Mass (m/z):510.66 (M^+ -18)
(2S,3R)-5-(4'-chloro-3'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 15),
Mass (m/z):496.10 (M^+ +1)
(2S,3R)-2-[2-(5-tert-butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 16),
Mass (m/z):536.11 (M^+ +1)
(2S,3R)-2-[2-(5-tert-butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 17),
Mass (m/z):530.09 (M^+ +1)
(2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 18),
Mass (m/z): 512.04(M^+ +1)
(2S,3R)-2-[2-(5-tert-butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 19),
Mass (m/z):518.14 (M^+ +1)
(2S,3R)-2-[2-(5-tert-butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 20),
Mass (m/z):534.09 (M^+)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 21),
Mass (m/z):512.08 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 22),
Mass (m/z): 458.14(M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 23),
Mass (m/z): 492.07(M^+ +1)
(2S,3R)-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. 24),
Mass (m/z):489.11 (M^+ +1)
(2S,3R)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 25),
Mass (m/z):458.14 (M^+ +1)
(2S,3R)-5-(4'-ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 26),
Mass (m/z): 472.15(M^+ +1)
(2S,3R)-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. 27),
Mass (m/z):492.08 (M^+ +1)
(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 28),
Mass (m/z):478.09 (M^+ +1)

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyrimidin-5-ylphenyl)pentanoic acid (Compound No. 29),
Mass (m/z):446.12 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 30),
Mass (m/z): 448.25 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyridin-3-ylphenyl)pentanoic acid (Compound No. 31),
Mass (m/z): 445.23(M^+ +1)
(2S,3R)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 32),
Mass (m/z):502.19 (M^+ +1)
(2S,3R)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 33),
Mass (m/z):489.0(M^+ +1)
(2S,3R)-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 34),
Mass (m/z):473.0(M^+ +1)
(2S,3R)-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 35),
Mass (m/z): 448.0 (M^+ +1)
(2S,3R)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 36),
Mass (m/z): 505.0 (M^+ +1)
(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 37),
Mass (m/z):509.0 (M^+ +1)
(2S,3R)-3-hydroxy-2-{2-[7-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 38),
Mass (m/z):582.0 (M^+ +1)
(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 39),
Mass (m/z): 511.0 (M^+ +1)
(2S,3R)-2-[2-(8-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 40),
Mass (m/z): 493.3(M^+ +1)
(2S,3R)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 41),
Mass (m/z):489.0 (M^+ +1)
(2S,3R)-3-hydroxy-2-{2-[5-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 42),
Mass (m/z): 582.0(M^+ +1)
(2S,3R)-5-(4'-chloro-3'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 43),
Mass (m/z):519.0 (M^+ +23)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-isobutyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 44),
Mass (m/z):490.0 (M^+ +1)
(2S,3R)-5-biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 45),
Mass (m/z): 444.0 (M^+ +1)

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 46),
Mass (m/z):476.0 (M^+ +1)
(2S,3R)-5-(3,3'-difluoro-4'-methoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 47),
Mass (m/z):510.0 (M^+ +1)
(2S,3R)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 48),
Mass (m/z):502.0 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1H-tetrazol-1-yl)phenyl]pentanoic acid (Compound No. 49),
Mass (m/z): 458.0 (M^+ +23)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 50),
Mass (m/z):493.0 (M^+ +1)
(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 51),
Mass (m/z): 498.0 (M^+ +23)
(2S,3R)-3-hydroxy-5-[4-(1-isobutyl-1H-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 52),
Mass (m/z):490.0 (M^+ +1)
(2S,3R)-5-biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 53),
Mass (m/z):444.0 (M^+ +1)
(2S,3R)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 54),
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 55),
Mass (m/z): 493.16(M^+ +1)
(2S,3R)-5-(4'-chloro-3-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 56),
Mass (m/z): 496.13 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[6-(4-methoxyphenyl)pyridin-3-yl]pentanoic acid (Compound No. 57),
Mass (m/z): 475.13 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 58),
Mass (m/z): 492.13 (M^+ +1)
(2S,3R)-5-[6-(4-chlorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 59),
Mass (m/z):479.12 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 60),
Mass (m/z): 476.16 (M^+ +1)
(2S,3R)-5-[4-(4-chlorophenyl)-2-thienyl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 61),
Mass (m/z):484.0 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)-2-thienyl]pentanoic acid (Compound No. 62),
Mass (m/z): 481.0(M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-{4-[4-(trifluoromethyl)phenyl]-2-thienyl}pentanoic acid (Compound No. 63),

Mass (m/z):518.0 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[4-(3-fluoro-4-methoxyphenyl)-2-thienyl]-3-hydroxypentanoic acid (Compound No. 64),
Mass (m/z): 498.0 (M^+ +1)
(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 65),
Mass (m/z):526.0 (M^+ +1)
(2S,3R)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 66),
Mass (m/z):526.0 (M^+ +1)
(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 67),
Mass (m/z): 492.0(M^+ +1)
(2S,3R)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 68),
Mass (m/z): 542.29(M^+ +1)
(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 69),
Mass (m/z):548.54 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[2-fluoro-5-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 70),
Mass (m/z): 493.30(M^+ +1)
(2S,3R)-5-(4'-chloro-4-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 71),
Mass (m/z):495.72 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[6-fluoro-4'-(trifluoromethyl)biphenyl-3-yl]-3-hydroxypentanoic acid (Compound No. 72),
Mass (m/z):530.13 (M^+ +1)
(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[4-fluoro-3-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 73),
Mass (m/z):493.37 (M^+ +1)
(2S,3R)-5-(4'-chloro-6-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 74),
Mass (m/z):496.26 (M^+ +1)
(2S,3R)-5-(3',6-difluoro-4'-methoxybiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 75),
Mass (m/z):509.77 (M^+ +1)
(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 76),
Mass (m/z): 492.56(M^+ +1)
(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 77),
Mass (m/z):480.0 (M^+ +1)
(2S,3R)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 78),
Mass (m/z): 462.19 (M^+ +1)
(2S,3R)-2-[2-(5-chloro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 79),
Mass (m/z):546.32 (M^+ +1)
(2S,3R)-2-[2-(4-fluoro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 80),
Mass (m/z):529.25 (M^+ +1)

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 81),
Mass (m/z): 498.27(M^+ +1)
(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. 86),
Mass (m/z): 474.87(M^+ +1)
(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. 87),
Mass (m/z): 478.09(M^+ +1)
(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.88).
Mass (m/z): 474.88(M^+ +1)

EXAMPLE-2

Synthesis of (2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid (Compound No. 82)

Step a: Synthesis of 3-{2-[(3aS,5R,6S,6aS)-2,2-dimethyl-5-(2-phenylethyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-yl]ethyl}-1,2,3-benzotriazin-4(3H)-one

To the solution of 3-(2-{(3aS,5R,6S,6aS)-5-[(E)-2-(4-bromophenyl)vinyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one (0.3g), obtained from step j of Example 1, in a solvent mixture of tetrahydrofuran: methanol (10mL:10 mL) was added palladium/carbon (0.2 g, 10%) at room temperature and the reaction mixture was hydrogenated at the pressure of 35 psi for 4 h in Paar apparatus. The reaction mixture was filtered through celite pad and the residue was washed with methanol. The filtrate was concentrated to afford the title compound (0.3 g).

Mass (m/z):421 (M^+)

Step b: Synthesis of 3-{2-[(2R,3R,4S,5R)-4,5-dihydroxy-2-(2-phenylethyl)tetrahydrofuran-3-yl]ethyl}-1,2,3-benzotriazin-4(3H)-one

Perchloric acid (0.2 mL) was added to a solution of 3-{2-[(3aS,5R,6S,6aS)-2,2-dimethyl-5-(2-phenylethyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-yl]ethyl}-1,2,3-benzotriazin-4(3H)-one (0.3g) in acetonitrile (4 mL) and water (0.3 mL) at room temperature. The reaction mixture was heated to 55°C for 30 min. Reaction mixture was then quenched using sodium bicarbonate solution. The solvents were evaporated at reduced pressure. The residue thus obtained was taken in ethyl acetate and water. Organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was concentrated under the reduced pressure to yield the title compound (0.3 g).

Step c: Synthesis of (2S,3R)-3-(formyloxy)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid

To a solution of 3-{2-[(2R,3R,4S,5R)-4,5-dihydroxy-2-(2-phenylethyl)tetrahydrofuran-3-yl]ethyl}-1,2,3-benzotriazin-4(3H)-one (0.3 g) in a tert- butanol:tetrahydrofuran (3mL:3mL) at 0°C was added a solution of sodium metaperiodate (0.673 g in 3mL of water). The reaction mixture was stirred for 2 h at same temperature and potassium permangnate (0.025 g) was added at 0°C. After stirring, the reaction mixture for additional 6h at room temperature, reaction mixture was evaporated on rota-evaporator, the residue was taken into water and extracted with ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure, to afford the title compound (0.3 g).

Step d: Synthesis of (2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid

Potassium carbonate (0.11 g) was added to a solution of (2S,3R)-3-(formyloxy)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid (0.3 g) in methanol (4mL) and tetrahydrofuran (4mL) at 0°C. The reaction mixture was stirred at room temperature for 3h. Solvents were evaporated and the residue was taken into water and ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure obtain a residue which was purified by column chromatography over silica gel using 10% methanol in dichloromethane as eluant to afford the title compound (0.020g).

Mass (m/z):368.0 (M^+ +1)

^{1}HNMR (CD_3OD): 8.31 (d, 1H, 8Hz), 8.15 (d, 1H, 8Hz), 8.06- 8.02 (m, 1H), 7.91- 7.89 (m, 2H), 7.62 (d, 2H, 8Hz), 7.36 (d, 1H, 8Hz), 7.21-7.07 (m, 1H), 4.57- 4.52 (m, 2H), 3.78-3.76 (m, 1H), 2.76 -2.75 (m, 1H), 2.57 - 2.49 (m, 2H), 2.29- 2.27 (m, 2H), 1.74- 1.71 (m, 2H).

Analogue of (2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid was prepared similarly

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-phenylpentanoic acid (Compound No. 83)

Mass (m/z): 368.07 (M^+ +1)

EXAMPLE-3

Synthesis of (2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4 (trifluoromethyl)phenyl]pentanoic acid (Compound No.84)

Step a: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-1,2-O-isopropylidene-β-D-lyxofuranose

A mixture of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-hydroxyethyl)-1,2-O-isopropylidene-β-D-lyxofuranose (0.14g), obtained from step f of Example 1, triphenylphosphine (0.080g) and

pthalimide (0.045g) were taken in a round bottom flask and dried in high vacuum for 10 min. Then vacuum was released under nitrogen atmosphere and tetrahydrofuran (5mL) was added to the reaction mixture. The reaction mixture was cooled to 0°C and diethyl azodicarboxylate (0.1 mL) was added slowly. The reaction mixture was stirred for 30 min at same temperature and then quenched with water and extracted with ethyl acetate. Organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated. The residue thus obtained was purified by column chromatography over silica gel using 30 % ethyl acetate in hexane as eluant to afford the title compound (0.11g).

Mass (m/z): 608(M^+ +23)

Step b: Synthesis of 3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-1,2-O-isopropylidene-β-D-lyxofuranose

To a solution of compound (0.060g), obtained from step a above, in dry tetrahydrofuran (2 mL) at 0°C, was added tetra butyl ammonium fluoride (0.2 mL). The resulting mixture was initially stirred at the 0°C for 1h and then at room temperature for 4h. The reaction mixture was cooled to 0°C, quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulphate and concentrated. The residue thus obtained was purified by column chromatography over silica gel using 60% ethyl acetate in hexane as eluant to furnish the title compound (0.4 g).

Step c: Synthesis of (5S)-3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4,5-O-isopropylidene-D-arabino-pentodialdo-5,2-furanose

In a three neck round bottom flask, oxalyl chloride (0.6 mL) and dichloromethane (20 mL) were placed and cooled to -78^{0}C. Dimethylsulfoxide (1mL) was added drop wise to the reaction mixture. The reaction mixture was warmed to -35°C for 5 to 10 min and again cooled to -78°C. 3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-1,2-O-isopropylidene-β-D-lyxofuranose (1 g) in dichloromethane (5mL) was added slowly while maintaining the same temperature. The reaction mixture was stirred for 45 min till reaction temperature reached to -35°C. The reaction mixture was again cooled to -78°C and triethylamine (2.4 mL) was added. The reaction mixture was stirred for additional 30 min and the temperature was allowed to reach to -35°C. Reaction mixture was quenched with saturated solution of ammonium chloride and extracted with dichloromethane. The combined organic layer was washed with water and brine solution, dried over anhydrous sodium sulphate and concentrated to furnish the title compound (1.0 g).

Step d: Synthesis of 2-{2-[(3aS,5R,6S,6aS)-2,2-dimethyl-5-{(E)-2-[4-(trifluoromethyl)phenyl]vinyl}tetrahydrofuro[2,3-d][1,3]dioxol-6-yl]ethyl}-1H-isoindole-1,3(2H)-dione

To the suspension of triphenyl[4-(trifluoromethyl)benzyl]phosphonium bromide (0.795 g) in dimethylsulphoxide (5 mL), potassium tert-butoxide (0.292g) was added. (5S)-3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4,5-O-isopropylidene-D-arabino-pentodialdo-5,2-furanose (0.5 g) in tetrahydrofuran (7 mL) was added drop wise after 20 min, and reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with water and extracted with ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure and the residue thus obtained was purified by column chromatography using 30% ethyl acetate in hexane as eluant to furnish the title compound (0.25g).

Mass (m/z):487 (M^+)

Step e: Synthesis of 2-{2-[(3aS,5R,6S,6aS)-2,2-dimethyl-5-{2-[4-(trifluoromethyl)phenyl]ethyl}tetrahydrofuro[2,3-d][1,3]dioxol-6-yl]ethyl}-1H-isoindole-1,3(2H)-dione

10% Palladium on charcoal (0.2 g) was added to the solution of compound (0.25g), obtained from step d above, in ethyl acetate(20 mL) at room temperature and the reaction mixture was hydrogenated at the pressure of 50 psi for 4 h in Paar apparatus. The reaction mixture was filtered through celite pad and the residue was washed with methanol. The filtrate was concentrated to afford the title compound (0.225 g).

Step f: Synthesis of 2-{2-[(2R,3R,4S,5R)-4,5-dihydroxy-2-{2-[4-(trifluoromethyl)phenyl]ethyl}tetrahydrofuran-3-yl]ethyl}-1H-isoindole-1,3(2H)-dione

Perchloric acid (0.2 mL) was added to a solution of compound (0.225 g), obtained from step e above, in acetonitrile (4mL), water (1 mL) and tetrahydrofuran (0.5 mL) at room temperature. The reaction mixture was heated to 55°C for 30 min. Reaction Mixture was then quenched using sodium bicarbonate solution. The solvents were evaporated at reduced pressure. The residue thus obtained was taken in ethylacetate and water. Organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was concentrated under the reduced pressure to yield the title compound (0.22g).

Step g: Synthesis of (1R,2S)-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-formyl-1-{2-[4-(trifluoromethyl)phenyl]ethyl}butyl formate

A solution of sodium metaperiodate (0.313 g in 1 mL of water) was added to the solution of 2-{2-[(2R,3R,4S,5R)-4,5-dihydroxy-2-{2-[4-(trifluoromethyl)phenyl]ethyl}tetrahydrofuran-3-yl]ethyl}-1H-isoindole-1,3(2H)-dione (0.22g) in a methanol:tetrahydrofuran(3 mL:1 mL) at

0°C. The reaction mixture was stirred for 2 h at same temperature. After stirring, the reaction mixture for additional 6h at room temperature, reaction mixture was evaporated on rotavapour, the residue was taken into water and extracted with ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure, to afford the title compound (0.22 g).

Step h: Synthesis of (2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-(formyloxy)-5-[4-(trifluoromethyl)phenyl]pentanoic acid

To a solution of compound (0.22g), obtained from step g above, in a solvent mixture of acetonitrile:water (3mL:1mL) at 0°C, were added sodium dihydrogenphosphate (0.021g), sodium chlorite (0.081g) and hydrogen peroxide (1mL, 30% in water). The reaction mixture was stirred for 2 h at room temperature. Solvents were evaporated under reduced pressure to obtain a residue. Ethyl acetate and water were added to the resulting residue. Organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure, to afford the title compound (0.2 g).

Step i: Synthesis of (2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(trifluoromethyl)phenyl]pentanoic acid

Potassium carbonate (0.178 g) was added to a solution of compound (0.2g), obtained from step h above, in methanol (7 mL) at 0°C. The reaction mixture was stirred at room temperature for 3h. Solvents were evaporated and the residue was taken into water and ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure obtain a residue which was purified by column chromatography over silica gel using 10 % methanol in dichloromethane as eluant to afford the title compound (0.090 g).

Mass (m/z): 458.0(M^+ +23)

^{1}HNMR (CD_3OD): 7.83 (q, 2H, J=3.1 Hz), 7.71 (t, 2H, J=3.2 Hz), 7.51 (d, 2H, J=7.6 Hz), 7.28 (d, 2H, J=7.9 Hz), 3.95-3.76 (m, 3H), 2.93-2.55 (m, 3H), 2.14-1.75 (m, 4H)

Analogue of (2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(trifluoromethyl)phenyl]pentanoic acid was prepared similarly

(2S,3R)-5-(4-tert-butylphenyl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.85)

Mass (m/z):424.0 (M^+ +1)

EXAMPLE-4

Synthesis of (2R,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 89)

Step a: Synthesis of 1,2:5,6-Di-O-isopropyliden-α-D-ribo-3-hexulo-furanose

Oxalyl chloride (25.16mL) and dichloromethane (200ml) were taken in a three neck round bottom flask and cooled to -75^{0}C under nitrogen atmosphere. Then dimethylsulfoxide (27.3 mL) was added dropwise slowly maintaining the temperature at -70^{0}C. The reaction mixture was stirred for 30 min at the same temperature then Diacetone-α-D-Glucose (50 g) in dichloromethane (500 mL) was charged slowly maintaining the temperature at -70^{0}C. After 20 min, triethylamine (80 mL) was added dropwise to the above mixture at the same temperature. Saturated solution of ammonium chloride in water (500 ml) was charged to the reaction mixture after 30 min and temperature was allowed to rise up to room temperature. Reaction mixture was extracted with dichloromethane. Organic layer was dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure to afford the title compound (45 g).

Step b : Synthesis of 1,2:5,6-Di-O-isopropylidene-3-deoxy-3-(2-ethoxy-2-oxoethylidene)- α -D-ribo-hexofuranose

To the suspension of sodium hydride (0.155 g, 60% in oil.) in tetrahydrofuran (5 mL) at 0^0 C was charged triethyl phosphonoacetate (1.55 mL).After 20 min, a solution of 1,2:5,6-Di-O-isopropyliden-α-D-ribo-3-hexulo-furanose (1 g)in tetrahydrofuran (3 mL) was added drop wise and reaction mixture was stirred for 1 h at the same temperature. Saturated solution of ammonium chloride was added to reaction mixture. The resulting mixture was extracted with ethyl acetate. Combined extracts were dried over anhydrous sodium sulphate and evaporated under the reduced pressure to yield a residue which was purified by column chromatography over silica gel using 30 % ethyl acetate in hexane as eluant to afford the title compound (1.3 g).

Mass (m/z): 351.1(M^+ +23)

Step c: Synthesis of 1,2:5,6-Di-O-isopropylidene-3-deoxy-3-(2-ethoxy-2-oxoethyl)- α -D-allofuranose

10% Palladium on charcoal (0.05 g) was added to the solution of compound (0.15 g), obtained from step b above, in ethyl acetate (10 mL) at room temperature and hydrogen was supplied at the pressure 50 psi for 4h. The reaction mixture was filtered through celite pad and the residue was washed with ethylacetate. The filtrate was concentrated to afford the title compound (0.12g).

Mass (m/z): 353.2 (M^+ +1).

Step d: Synthesis of 3-deoxy-3-(2-ethoxy-2-oxoethyl)-1,2-O-isopropylidene-α-D-allofuranose

30 % Perchloric acid (4 mL) was added to a solution of 1,2:5,6-Di-O-isopropylidene-3-deoxy-3-(2-ethoxy-2-oxoethyl)- α -D-allofuranose (2.0 g) in tetrahydrofuran (20 mL) at -5°C -0°C. The reaction mixture was stirred for 5 h at -5°C -0°C and then quenched with saturated solution of sodium bicarbonate (20 mL).Solvents were evaporated, ethyl acetate and water were added to the resulting residue. Organic layer was separated, washed with brine, dried over anhydrous sodium sulphate and concentrated to afford 1.5 g of the title compound.

Mass (m/z):313.2 (M^+ +1)

Step e: Synthesis of 3-deoxy-3-(2-ethoxy-2-oxoethyl)-1,2-O-isopropylidene-α-D-ribo-pentodialdo-1,4-furanose

To a solution of compound (1.5 g), obtained from step d above, in methanol (15 mL) was added aqueous solution of sodium periodate (1.65 g in 10 mL of water) at 0°C. The reaction mixture was stirred for 3h from 0°C to room temperature. Solvents were evaporated. Ethyl acetate and water were added to the residue. Organic layer was separated, washed with brine, dried over anhydrous sodium sulphate and concentrated to afford the title compound (0.9g).

Mass (m/z):259.2 (M^+ +1)

Step f: Synthesis of ethyl {(3aR,5R,6R,6aR)-5-[(E)-2-(4-bromophenyl)vinyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}acetate

To the suspension of (4-bromobenzyl)triphenylphosphonium bromide (2.67g) in dimethylsulphoxide (15 mL), potassium tert-butoxide (0.508g) was added at 0^0C. After stirring the reaction mixture for 30 min at room temperature, a solution of compound (0.9 g), obtained from step e above, in tetrahydrofuran (5 mL) was added drop wise at 0^0C. The reaction mixture was stirred for 2h from (0^0C to room temperature), quenched with ice cold water. Solvents were evaporated, ethyl acetate and water were added to resulting residue. Organic layer was separated, washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure and the residue thus obtained was purified by column chromatography using 10 % ethyl acetate in hexane as eluant to furnish the title compound (1.0 g).

Mass (m/z):413.3 (M^+ +1)

Step g: Synthesis of ethyl {(3aR,5R,6R,6aR)-5-[(E)-2-(4'-chlorobiphenyl-4-yl)vinyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}acetate

A mixture of compound (1.0g), obtained from step f above, (4-chlorophenyl)boronic acid (0.76 g), tetrakistriphenylphosphinepalladium (0) (0.14 g) and potassium carbonate (1.0 g) in dry dimethylformamide (10 mL) was heated at 110°C for 4 h. Ethyl acetate and water were added to the reaction mixture. Organic layer was separated,washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure to

obtain a residue which was purified by column chromatography over silica gel using 12 % ethyl acetate in hexane as eluant to afford the title compound (0.9 g).

Mass (m/z):465.2 (M^+ +23)

Step h: Synthesis of ethyl {(3aR,5R,6R,6aR)-5-[2-(4'-chlorobiphenyl-4-yl)ethyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}acetate

To the solution of compound (0.8 g), obtained from step g above, in ethyl acetate (15 mL) was added 10% Palladium on charcoal (0.25 g) at room temperature. The system was evacuated with hydrogen and the reaction mixture was stirred for 4 h at room temperature under hydrogen atmosphere. The reaction mixture was filtered through celite pad and concentrated to afford the title compound (0.75 g).

Mass (m/z):415.4 (M^+ -28)

Step i: Synthesis of 2-{(3aR,5R,6R,6aR)-5-[2-(4'-chlorobiphenyl-4-yl)ethyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethanol

To a solution of compound (0.75g), obtained from step h above, in tetrahydrofuran (15 mL) was added, lithium aluminium hydride (0.096 g) at 0^0C. The resulting mixture was stirred for 3h at same temperature, saturated solution of ammonium chloride was then added. The reaction mixture was then filtered through silica gel (100-200 mesh) and concentrated. Ethyl acetate and water was added to the resulting residue. Organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate, filtered, concentrated under reduced pressure to afford the title compound (0.65 g).

Mass (m/z):425.2 (M^+ +23)

Step j: Synthesis of 2-{(3aR,5R,6R,6aR)-5-[2-(4'-chlorobiphenyl-4-yl)ethyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl methanesulfonate

Triethylamine (0.43 ml) and methanesulfonyl chloride (0.21 mL) were added to solution of the compound (0.6 g) obtained from step i above, in dichloromethane (15 mL) at 0°C. The reaction mixture was stirred at room temperature for 2 h. Dichloromethane and water were added to reaction mixture. Organic layer was separated, washed with water, dried and concentrated under reduced pressure to furnish the title compound (0.6g).

Step k: Synthesis of 2-(2-{(3aR,5R,6R,6aR)-5-[2-(4'-chlorobiphenyl-4-yl)ethyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1H-isoindole-1,3(2H)-dione

Potassium phthalimide (0.051 g) was added in one portion to a stirred solution of the compound (0.12 g), obtained from step j above, in dimethylformamide (5 mL) at room temperature under nitrogen atmosphere. The resulting solution was heated at 50 °C for about 14 h and then cooled to room temperature. Ethyl acetate and water were added to the reaction mixture. The Organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate. The

organic phase evaporated to dryness under reduced pressure. The residue thus obtained was purified by column chromatography using 30 % ethyl acetate in hexane as eluant to furnish the title compound (0.1 g).

Mass (m/z): 549.5($M^+ + NH_4^+$)

Step l: Synthesis of 2-(2-{(2R,3S,4R,5S)-2-[2-(4'-chlorobiphenyl-4-yl)ethyl]-4,5-dihydroxytetrahydrofuran-3-yl}ethyl)-1H-isoindole-1,3(2H)-dione

Trifluoroacetic acid (1mL) and water (0.5 mL) were added to compound (0.04g), obtained from step k above. The reaction mixture was stirred at room temperature for 2h. The solvents were evaporated at reduced pressure. The residue thus obtained was taken in ethyl acetate and water. Organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was concentrated under the reduced pressure to yield the title compound (0.028 g).

Step m: Synthesis of (2R,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-(formyloxy)pentanoic acid

To a solution of 2-(2-{(2R,3S,4R,5S)-2-[2-(4'-chlorobiphenyl-4-yl)ethyl]-4,5-dihydroxy-tetrahydrofuran-3-yl}ethyl)-1H-isoindole-1,3(2H)-dione (0.028g) in a tert- butanol:water (2:3; 1.3 mL) was added sodium metaperiodate (0.051 g) at room temperature. The reaction mixture was stirred for 2 h at same temperature and potassium permangnate (0 .001 g) was added at 0°C. After stirring, the reaction mixture for additional 6h at room temperature, reaction mixture was evaporated on rota-evaporator, the residue was taken into water and extracted with ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure, to afford the title compound (0.025 g).

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

Potassium carbonate (0.007g) was added to a solution of compound (0.025 g, obtained from step m) in methanol (1 mL) at 0°C. The reaction mixture was stirred at room temperature for 3h. Solvents were evaporated and the residue was taken into water and ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure obtain a residue which was purified by column chromatography over silica gel using 10 % methanol in dichloromethane as eluant to afford the title compound (0.014 g).

Mass (m/z):478.2 (M^+ +1)

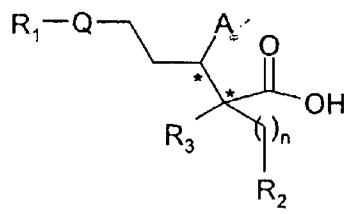
^{1}**HNMR (CD_3OD):** 7.83 (q, 2H, J=4Hz), 7.77 (q, 2H, J=4Hz), 7.56 (d, 2H, J=8Hz), 7.48 (d, 2H, J=8Hz), 7.40 (d, 2H, J= 8Hz), 7.26 (d, 1H, J=8Hz), 3.83-3.70 (m, 3H), 2.85-2.49 (m, 3H), 1.92-1.70(m, 4H)

Assay for Matrix Metallo Proteinases (MMPs)

NCEs/standards were prepared (stock 10 mM) in 100% DMSO and subsequent dilutions were made in 50% DMSO-50% TCNB (50 mM Tris, 10 mM $CaCl_2$, 150 mM NaCl, 0.05% Brij-35, pH 7.5). 1 µl of the compound and 88 µl of TCNB was added to wells of 96 well plate to achieve the desired final concentration of NCE (final DMSO concentration should not exceed 0.5%). 1 µl of activated, recombinant MMPs was added to each well (20-100 ng/100 µl reaction mixture) except the "negative well". (MMP-1, 9 &14 enzymes require prior activation. For this, supplied enzyme was incubated with either APMA, final concentration 1 mM, for a time period of 1 hr at 37°C). Incubation was done at room temperature for 4-5 min. Reaction was initiated with 10 µl of 100 µM substrate (ES001: Aliquots were freshly diluted in TCNB; stock: 2 mM) and increase in florescence was monitored at excitation wavelength 320 nm followed by emission at 405 nm for 25-30 cycles. Increase in florescence (RFU) was calculated for positive, negative and NCE/standard wells. The percent inhibition compared to controls was calculated and IC_{50} values determined using Graph-prism software.

WE CLAIM:

1. A compound having the structure of Formula I



Formula I

wherein

* denotes stereogenic (asymmetric) centre of defined configuration;

n is an integer from 1 to 5;

R_1 is hydrogen or 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, $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$.

Q is optionally substituted aryl or heteroaryl.

2. A compound selected from:

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

(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-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 2),

(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. 3),

(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. 4),

(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. 5),

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

(2*S*,3*R*)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 7),

(2*S*,3*R*)-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. 8),

(2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 9),

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

(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 11),

(2*S*,3*R*)-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. 12),

(2*S*,3*R*)-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. 13),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 14),

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

(2*S*,3*R*)-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. 16),

(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. 17),

(2*S*,3*R*)-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. 18),

(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. 19),

(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. 20),

(2*S*,3*R*)-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. 21),

(2*S*,3*R*)-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. 22),

(2*S*,3*R*)-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. 23),

(2*S*,3*R*)-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. 24),

(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 25),

(2*S*,3*R*)-5-(4'-ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 26),

(2*S*,3*R*)-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. 27),

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 28),

(2*S*,3*R*)-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. 29),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 30),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyridin-3-ylphenyl)pentanoic acid (Compound No. 31),

(2*S*,3*R*)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 32),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 33),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 34),

(2*S*,3*R*)-3-hydroxy-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 35),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 36),

(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 37),

(2*S*,3*R*)-3-hydroxy-2-{2-[7-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 38),

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 39),

(2*S*,3*R*)-2-[2-(8-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 40),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 41),

(2*S*,3*R*)-3-hydroxy-2-{2-[5-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 42),

(2*S*,3*R*)-5-(4'-chloro-3'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 43),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-isobutyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 44),

(2*S*,3*R*)-5-biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 45),

(2*S*,3*R*)-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. 46),

(2*S*,3*R*)-5-(3,3'-difluoro-4'-methoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 47),

(2*S*,3*R*)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 48),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1*H*-tetrazol-1-yl)phenyl]pentanoic acid (Compound No. 49),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 50),

(2*S*,3*R*)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 51),

(2*S*,3*R*)-3-hydroxy-5-[4-(1-isobutyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 52),

(2*S*,3*R*)-5-biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 53),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 54),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 55),

(2*S*,3*R*)-5-(4'-chloro-3-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 56),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[6-(4-methoxyphenyl)pyridin-3-yl]pentanoic acid (Compound No. 57),

(2*S*,3*R*)-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. 58),

(2*S*,3*R*)-5-[6-(4-chlorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 59),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 60),

(2*S*,3*R*)-5-[4-(4-chlorophenyl)-2-thienyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 61),

(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)-2-thienyl]pentanoic acid (Compound No. 62),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-{4-[4-(trifluoromethyl)phenyl]-2-thienyl}pentanoic acid (Compound No. 63),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-(3-fluoro-4-methoxyphenyl)-2-thienyl]-3-hydroxypentanoic acid (Compound No. 64),

(2*S*,3*R*)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 65),

(2*S*,3*R*)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 66),

(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 67),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 68),

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 69),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[2-fluoro-5-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 70),

(2*S*,3*R*)-5-(4'-chloro-4-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 71),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[6-fluoro-4'-(trifluoromethyl)biphenyl-3-yl]-3-hydroxypentanoic acid (Compound No. 72),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-fluoro-3-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 73),

(2*S*,3*R*)-5-(4'-chloro-6-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 74),

(2*S*,3*R*)-5-(3',6-difluoro-4'-methoxybiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 75),

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

(2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 77),

(2*S*,3*R*)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 78),

(2*S*,3*R*)-2-[2-(5-chloro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 79),

(2*S*,3*R*)-2-[2-(4-fluoro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 80),

(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 81),

(2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid (Compound No. 82),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-phenylpentanoic acid (Compound No. 83),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4 (trifluoromethyl)phenyl]pentanoic acid (Compound No. 84),

(2*S*,3*R*)-5-(4-*tert*-butylphenyl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.85).

3. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of the proceeding claims together with pharmaceutically acceptable carrier, excipients or diluents.

Dated this the **18th** day of **August, 2006.**

For Ranbaxy Laboratories Limited

Sushil Kumar Patawari
Company Secretary

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22 AUG 2006

ABSTRACT

MATRIX METALLOPROTEINASE INHIBITORS

The present invention relates to certain β-hydroxy and amino substituted carboxylic acids as matrix metalloprotease inhibitors, particularly diastereomerically pure β-hydroxy carboxylic acids 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, perodontitis, 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.

Docket No. RLL-895

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/IB2007/053340
  - Other (specify) ____ _____ _____ _____ _____

Title of the Invention:

MATRIX METALLOPROTEINASE INHIBITORS

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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;

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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.

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(54) Title: MATRIX METALLOPROTEINASE INHIBITORS

(57) Abstract: The present invention relates to β-hydroxy and amino substituted carboxylic acids, which act as matrix metalloprotease inhibitors, particularly diastereomerically pure β-hydroxy carboxylic acids, corresponding processes for the synthesis of and pharmaceutical compositions containing the compounds of the present invention. Compounds of the present invention are useful in the treatment of various inflammatory, autoimmune and allergic diseases, such as methods of treating asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, psoriasis, pulmonary fibrosis, wound healing disorders, pulmonary inflammation, acute respiratory distress syndrome, perodontitis, 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 the over-expression and over- activation of a matrix metalloproteinase using the compounds.

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MATRIX METALLOPROTEINASE INHIBITORS

Field of the Invention

The present invention relates to certain β-hydroxy- and amino-substituted carboxylic acids as matrix metalloprotease inhibitors, particularly diastereomerically pure β-hydroxy-carboxylic acids and to processes for their syntheses.

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, wound healing disorders, pulmonary inflammation, acute respiratory distress syndrome, perodontitis, 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 the over-expression and over-activation of a matrix metalloproteinase using the compounds.

Background of the Invention

Metalloproteinases (MMPs) are a naturally occurring superfamily of proteinases (enzymes) found in most mammals. The superfamily is composed of at least 26 members of zinc-containing enzymes produced by many cell types and sharing structural and functional features. Based on structural and functional considerations proteinases have been classified into different families and subfamilies (Vartak et al., (2007), *J. Drug Targeting*, 15, 1-20; and Hopper, (1994), *FEBS*, 354, 1-6), such as collagenases (MMP-1, -8 and -13), gelatinases (MMP-2, and -9), metalloelastases (MMP-12), the MT-MMPs (MMP-14, -15, -16, -17, - 24 and 25), matrilysins (MMP-7 and -26), stromelysins (MMP-3, -10 and -11) and sheddases such as TNF-converting enzymes (TACE, and ACE).

Metalloproteinases are believed to be important in 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 ability to hydrolyze various components of tissue or matrix. Apart from their role in degrading connective tissue, MMPs are involved in the activation of zymogen (pro) forms of other MMPs thereby inducing MMP activation. They are also involved in the biosynthesis of TNF-alpha which is implicated in many pathological conditions.

MMP-12, also known as macrophage elastase or metalloelastase, is expressed in activated macrophages and has been shown to be secreted from alveolar macrophages from smokers as well as in foam cells in atherosclerotic lesions. MMP-12 knockout mouse studies have shown the development of significant emphysema, thus supporting its role in COPD. MMP-9 (gelatinase B, 92 kDa type IV collagenase) is one member of the MMP family that is released as a proenzyme and subsequently activated *via* a protease cascade *in vivo*.

The concentration of MMP-9 is increased in diseases like asthma, interstitial pulmonary fibrosis (IPF), adult respiratory distress syndrome (ARDS), and in chronic obstructive pulmonary disease (COPD). Because of its proteolytic ability, MMP-9 has been implicated in tissue remodelling of the airways and lungs in chronic inflammatory diseases such as severe asthma and COPD. MMP-9 is also likely to be physiologically important because of its ability to regulate the digestion of components of the extracellular matrix as well as the activity of other proteases and cytokines. MMP-9 is secreted in neutrophils, macrophages, osteoclasts, which are easily induced by cytokines and growth factors, and plays a role in various physiological and pathological processes.

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

Inhibition of the activity of one or more MMPs may be of benefit in treatment of various inflammatory, autoimmue and allergic diseases such as, inflammation of the joint, inflammation of the GI tract, inflammation of the skin, collagen remodeling, wound healing disorders etc.

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 2004/110974 discloses compounds and their physiologically functional derivatives described as inhibitors of matrix metalloproteinase enzymes. WO 2004/113279 discloses alleged inhibitors of matrix metalloproteinase. WO 2005/026120

discloses compounds also described as inhibitors of matrix metalloproteinase. U.S. Patent No. 6,350,885 discloses tricyclic heteroaromatic compounds and their derivatives believed to be inhibitors of matrix metalloproteinases. WO 98/09940 discloses biphenyl butyric acids and their derivatives described as inhibitors of matrix metalloproteinases. *J. Med. Chem.*, (1968), vol. 11(6), 1139-1144 discloses the synthesis and anti-inflammatory activity of 4-(p-biphenylyl)-3-hydroxybutyric acid and related compounds. WO 96/15096 discloses substituted 4-biarylbutyric or 5-biarylpentanoic acids and derivatives as alleged matrix metalloproteinase inhibitors. WO 2006/090235 describes 5-phenyl-pentanoic acid derivatives described as matrix metalloproteinase inhibitors for the treatment of asthma and other diseases.

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.

Many drugs exist as asymmetric three-dimensional molecules i.e., chiral and will therefore have several stereoisomers depending upon the number of chiral centers present. The importance of evaluating new chemical entities having chiral centers as single isomers is to understand their effect on pharmacological and toxicological aspects. There are often pharmacodynamic, pharmacokinetic and/or toxicological differences between enantiomers / diastereomers. Even if natural physiological mediators are achiral, based on their target environment, their receptors/enzymes may demonstrate a preference for only one optically pure enantiomer of agonists, antagonists or inhibitors. From a pharmacokinetics point of view, chirality can have an influence on drug absorption, distribution, metabolism and elimination. Pure single isomers may also offer advantages in terms of these pharmacokinetic parameters thus enabling better developability of such molecules as drug candidates. It is also known that chirality has a significant effect of the physicochemical

properties and crystallinity of a chiral molecule which in turn have profound effects on the pharmacokinetics and developability of the molecule. Besides those mentioned above, regulatory principles guide one to preferably develop single isomers as drug candidates in order to avoid any pharmacological, pharmacokinetic and toxicological problems that may arise due to interactions of an unwanted isomer with undesirable molecular targets.

In this context, synthetic strategies to produce pure single isomers offer advantages over analytical techniques of separation of isomer not only in terms of cost and efficiency but larger amounts of compound can be prepared for elaborate pharmaceutical testing. Thus, compounds of present invention, which are single chiral isomers, have improved potency, improved pharmacokinetics and /or improved physicochemical properties as compared to racemic compounds.

The present invention is directed to overcoming problems encountered in the art.

Summary of the Invention

The present invention relates to β-hydroxy and amino substituted carboxylic acids, which act as matrix metalloprotease inhibitors, particularly diastereomerically pure β-hydroxy carboxylic acids, -corresponding processes for the synthesis of and pharmaceutical compositions containing the compounds of the present invention. The present invention relates to matrix metalloproteinase inhibitors useful as effective therapeutic or prophylactic agents in treatment of various inflammatory, autoimmune, and allergic diseases and other inflammatory disorders characterized by the over-expression and over-activation of a matrix metalloproteinase using the compounds.

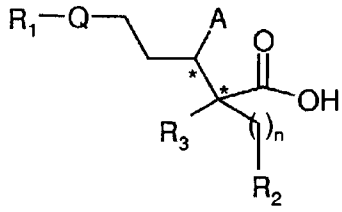
The present invention relates to compounds that act as dual MMP-9/12 inhibitors, which have desirable activity profiles and beneficial potency, selectivity and/or pharmacokinetic properties.

The present invention includes new chemical entities having chiral centers as single isomers. Synthetic strategies to produce pure single isomers that offer advantages over analytical techniques of separation of isomer not only in terms of cost and efficiency but also larger amount of compound can be prepared for elaborate pharmaceutical testing are also provided.

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.

Detailed Description of the Invention

The present invention relates to compounds having the structure of Formula I:



Formula I

wherein:

* denotes or represents a stereogenic or asymmetric center of defined configuration selected from (R, R), (S, S), (R, S) and (S,R);

n is an integer from 1 to 5;

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

R_2 is heterocyclyl, heteroaryl, 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;

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

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

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;

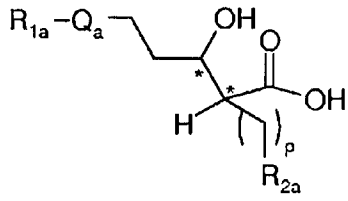
R_3 is hydrogen, fluorine, alkyl, cycloalkylalkyl or aralkyl;

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, $-NHSO_2R_4$;

Q is optionally substituted aryl or heteroaryl.

Compounds of formula I have particularly advantageous properties, which may include biological activities, such as modelling of LPS-incuded rat neutrophilia, selective inhibition of MMP-9 and MMP-12 activity, and inhibition of these activities without selectivity towards MMP-1 activity. Further, these advantageous properties may include solubilities which enhance preparation and administration of dosage forms, and improved bioavailability, as compared to known compounds, for example, those of WO 2005/026120.

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



(Ia)

wherein:

* denotes or represents a stereogenic or asymmetric center of defined configuration selected from (R, R), (S, S), (R, S) and (S,R);

p is an integer from 1 to 3;

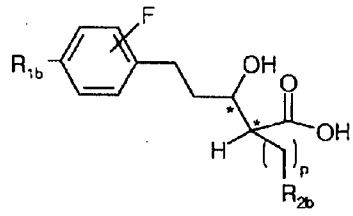
R_{1a} is optionally substituted aryl or heteroaryl;

R_{2a} is 5-6 membered N-containing heterocyclyl linked through N atom, which is optionally fused to aryl, heteroaryl or spirofused to cycloalkyl, which can optionally be futher substituted with one or more oxo group, alkyl, cycloalkyl, halo, alkoxy, trifluoroalkyl or aryl;

Q_a is optionally substituted 5 or 6 membered heteroaryl containing 1-3 heteroatom selected from O, N or S.

Compounds of formula Ia have particularly advantageous properties, which may include biological activities, such as modelling of LPS-incuded rat neutrophilia, selective inhibition of MMP-9 and MMP-12 activity, and inhibition of these activities without selectivity towards MMP-1 activity. Further, these advantageous properties may include solubilities which enhance preparation and administration of dosage forms, and improved bioavailability, as compared to known compounds, for example, those of WO 2005/026120.

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



(Ib)

wherein:

* denotes or represents a stereogenic or asymmetric center of defined configuration selected from (R, R), (S, S), (R, S) and (S,R);

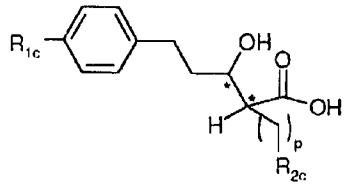
p is an integer from 1 to 3;

R_{1b} is optionally substituted phenyl or heteroaryl ; wherein optional substituents can be selected from with one or more alkyl, halo, alkoxy, trifluoroalkyl or aryl;

R_{2b} is 5-6 membered N-containing heterocyclyl linked through N atom, which is optionally fused to aryl, heteroaryl or spirofused to cycloalkyl, which can optionally be futher substituted with one or more oxo group, alkyl, cycloalkyl, halo, alkoxy, trifluoroalkyl or aryl.

Compounds of formula Ib have particularly advantageous properties, which may include biological activities, such as modelling of LPS-incuded rat neutrophilia, selective inhibition of MMP-9 and MMP-12 activity, and inhibition of these activities without selectivity towards MMP-1 activity. Further, these advantageous properties may include solubilities which enhance preparation and administration of dosage forms, and improved bioavailability, as compared to known compounds, for example, those of WO 2005/026120.

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



(Ic)

wherein:

* denotes or represents a stereogenic or asymmetric center of defined configuration selected from (R, R), (S, S), (R, S) and (S,R);

p is an integer from 1 to 3;

R_{1c} is optionally substituted phenyl, pyridyl, pyrimidyl, thienyl or pyrazolyl; wherein optional substitutent can be selected from with one or more alkyl, halo, alkoxy, trifluoroalkyl or aryl;

R_{2c} is 5-6 membered N-containing heterocyclyl linked through N atom, which is optionally fused to aryl, heteroaryl or spirofused to cycloalkyl, which can optionally be futher substituted with one or more oxo group, alkyl, cycloalkyl, halo, alkoxy, trifluoroalkyl or aryl.

In compounds of Formula Ic, R_{2c} represents 5-6 membered N-containing heterocyclyl linked through N atom, which is optionally fused to aryl, heteroaryl or spirofused to cycloalkyl, for example benzotriazinone, isoindoledione, pyrimidinedione, aza-spiro[4.5]decanedione, benzo-oxazinedione, imidazolidinedione or phthalazinone.

Compounds of formula Ic have particularly advantageous properties, which may include biological activities, such as modelling of LPS-incuded rat neutrophilia, selective inhibition of MMP-9 and MMP-12 activity, and inhibition of these activities without selectivity towards MMP-1 activity. Further, these advantageous properties may include solubilities which enhance preparation and administration of dosage forms, and improved bioavailability, as compared to known compounds, for example, those of WO 2005/026120.

The 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, diastereomers, conformational isomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier and optionally included excipients.

In one embodiment, the invention encompasses compounds of Formula (I), which may include, but are not limited to the following, for example

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

(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-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 2),

(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. 3),

(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. 4),

(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. 5),

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

(2*S*,3*R*)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 7),

(2*S*,3*R*)-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. 8),

(2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 9),

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

(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 11),

(2*S*,3*R*)-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. 12),

(2*S*,3*R*)-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. 13),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 14),

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

(2*S*,3*R*)-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. 16),

(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. 17),

(2*S*,3*R*)-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. 18),

(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. 19),

(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. 20),

(2*S*,3*R*)-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. 21),

(2*S*,3*R*)-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. 22),

(2*S*,3*R*)-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. 23),

(2*S*,3*R*)-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. 24),

(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 25),

(2*S*,3*R*)-5-(4'-ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 26),

(2*S*,3*R*)-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. 27),

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 28),

(2*S*,3*R*)-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. 29),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 30),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyridin-3-ylphenyl)pentanoic acid (Compound No. 31),

(2*S*,3*R*)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 32),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 33),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 34),

(2*S*,3*R*)-3-hydroxy-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 35),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 36),

(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 37),

(2*S*,3*R*)-3-hydroxy-2-{2-[7-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 38),

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 39),

(2*S*,3*R*)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid(Compound No. 40),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 41),

(2*S*,3*R*)-3-hydroxy-2-{2-[5-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 42),

(2*S*,3*R*)-5-(4'-chloro-3'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 43),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-isobutyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 44),

(2*S*,3*R*)-5-biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 45),

(2*S*,3*R*)-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. 46),

(2*S*,3*R*)-5-(3,3'-difluoro-4'-methoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 47),

(2*S*,3*R*)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 48),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1*H*-tetrazol-1-yl)phenyl]pentanoic acid (Compound No. 49),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 50),

(2*S*,3*R*)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 51),

(2*S*,3*R*)-3-hydroxy-5-[4-(1-isobutyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 52),

(2*S*,3*R*)-5-biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 53),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 54),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 55),

(2*S*,3*R*)-5-(4'-chloro-3-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 56),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[6-(4-methoxyphenyl)pyridin-3-yl]pentanoic acid (Compound No. 57),

(2*S*,3*R*)-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. 58),

(2*S*,3*R*)-5-[6-(4-chlorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 59),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 60),

(2*S*,3*R*)-5-[4-(4-chlorophenyl)-2-thienyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 61),

(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)-2-thienyl]pentanoic acid (Compound No. 62),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-{4-[4-(trifluoromethyl)phenyl]-2-thienyl}pentanoic acid (Compound No. 63),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-(3-fluoro-4-methoxyphenyl)-2-thienyl]-3-hydroxypentanoic acid (Compound No. 64),

(2*S*,3*R*)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 65),

(2*S*,3*R*)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 66),

(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 67),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 68),

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 69),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[2-fluoro-5-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 70),

(2*S*,3*R*)-5-(4'-chloro-4-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 71),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[6-fluoro-4'-(trifluoromethyl)biphenyl-3-yl]-3-hydroxypentanoic acid (Compound No. 72),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-fluoro-3-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 73),

(2*S*,3*R*)-5-(4'-chloro-6-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 74),

(2*S*,3*R*)-5-(3',6-difluoro-4'-methoxybiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 75),

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

(2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 77),

(2*S*,3*R*)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 78),

(2*S*,3*R*)-2-[2-(5-chloro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 79),

(2*S*,3*R*)-2-[2-(4-fluoro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 80),

(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 81),

(2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid (Compound No. 82),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-phenylpentanoic acid (Compound No. 83),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4(trifluoromethyl)phenyl]pentanoic acid (Compound No. 84),

(2*S*,3*R*)-5-(4-*tert*-butylphenyl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.85),

(2*S*,3*R*)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 90),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 91),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 92),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 93),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 94),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 95),

(2S,3R)-5-(2',4'-difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 97),

(2S,3R)-2-[2-(6-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 98),

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 99),

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-isopropylbiphenyl-4-yl)pentanoic acid (Compound No. 100),

(2S,3R)-5-(3'-chloro-4'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 101),

(2S,3R)-5-(4'-butylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 102),

(2S,3R)-5-(2'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 103),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 104),

(2S,3R)-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 105),

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 106),

(2S,3R)-5-[6-(3,4-difluorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 107),

(2S,3R)-5-[6-(4-chloro-3-fluorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 108),

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[6-(4-fluorophenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 109),

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[6-(3-fluoro-4-methylphenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 110),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 111),

(2S,3R)-2-[2-(8-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 112),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 113),

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 114),

(2S,3R)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 115),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 116),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 117),

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 118),

(2S,3R)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 119),

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 121),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 122),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 123),

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 124),

(2S,3R)-3-hydroxy-5-[4-(1-isobutyl-1H-pyrazol-4-yl)phenyl]-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 125),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 126),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 127),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 128),

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 129),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 130),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 131),

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 132),

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 133),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 134),

(2S,3R)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 135),

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 136),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 137),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 138),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 139),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 140),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 141),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 142),

(2*S*,3*S*)-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. 143),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 144),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 145),

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 146),

(2S,3R)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 147),

(2S,3R)-5-[4-(6-chloropyridin-3-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 148),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 149),

(2S,3R)-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 150),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 151),

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 152),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 153),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 154),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 155),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 156),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 157),

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 158),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 159),

(2S,3R)-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 160),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 161),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 162),

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 163),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 164),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 165),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 166),

(2S,3R)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 167),

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 168),

(2S,3R)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 169),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 170),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 171),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 172),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 173),

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 174),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 175),

(2S,3R)-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)-2-thienyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 176),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 177),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 178),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 179),

(2S,3R)-5-[4-(2-chloropyridin-3-yl)phenyl]-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 180),

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 181),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 182),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 183),

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 184),

(2*S*,3*R*)-3-hydroxy-5-[4-(2-methoxypyrimidin-5-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 185),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 186),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 187),

(2*S*,3*R*)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxypentanoic acid (Cmpound No. 188),

(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 189),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 190),

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 191),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 192),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 193),

(2*S*,3*R*)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(2-methoxypyrimidin-5-yl)phenyl]pentanoic acid (Compound No. 194),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(2-methoxypyrimidin-5-yl)phenyl]pentanoic acid (Compound No. 195),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl) ethyl]pentanoic acid (Compound No. 196),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 197),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-{2-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}pentanoic acid (Compound No. 198),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 199),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 200),

(2*S*,3*R*)-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 201),

(2*S*,3*R*)-2-[2-(2,4-dioxo-2*H*-1,3-benzoxazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 202),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]pentanoic acid (Compound No. 203),

(2S,3R)-5-(4-chloro-3-fluorophenyl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 204),

(2R,3S)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 205),

(2*R*,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. 206),

(2*R*,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. 207),

(2*S*,3*S*)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 208),

(2*S*,3*R*)-3-hydroxy-5-[4-(5-methylpyridin-2-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 209),

(2*S*,3*R*)-5-[4-(6-fluoropyridin-3-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 210),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 211),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 212),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 213),

(2*S*,3*R*)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 214),

(2*S*,3*R*)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 215),

(2*S*,3*R*)-5-(2',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 216),

((2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 217),

(2*S*,3*R*)-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 218),

(2*S*,3*R*)-3-hydroxy-5-[4-(2-methoxypyrimidin-5-yl)phenyl]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 219),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 220),

(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 221),

(2*S*,3*R*)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 222),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 223),

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 224),

(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 225),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-hydroxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid(Compound No. 226),

(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-{2-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}pentanoic acid (Compound No. 227),

(2*S*,3*R*)-2-[2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 228),

(2*S*,3*R*)-3-(acetyloxy)-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 229),

(2*S*,3*R*)-2-[2-(8-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid(Compound No. 230),

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(2,4-dioxo-2*H*-1,3-benzoxazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 231), and

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-(2-{[(2-hydroxyphenyl) carbonyl]amino}ethyl) pentanoic acid (Compound No. 232) .

In another embodiment, the present invention relates to a chiral auxiliary (4S)-4-benzyl-1,3-thiazolidin-2-one which would be of versatile utility for asymmetric synthesis. Chiral auxiliaries are utilized in a wide variety of synthetic transformations which include, but not limited to, asymmetric aldol condensation, stereoselective alkylation, stereoselective Diels-Alder reaction, stereoselective Michael reactions, stereoselective differentiation of enantiotopic groups in molecules bearing prochiral centers. The chiral auxiliary is used in stoichiometric amounts to induce the stereoselective formation of stereogenic centers.

In another embodiment, the present invention relates to the therapeutically effective dose of a compound of Formula I in combination with one or more of other therapeutic agents used for treating various inflammatory and allergic diseases. Examples of such therapeutic agents include, but are not limited to:

1) Anti-inflammatory agents, experimental or commercial (i) such as nonsteroidal anti-inflammatory agents piroxicam, diclofenac, propionic acids, fenamates, pyrazolones, salicylates, PDE-4/p38 MAP Kinase/Cathepsin inhibitors, CCR-3 antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists, Cell adhesion inhibitors (specially ICAM), adenosine 2a agonists (ii) leukotrienes LTC4/LTD4/LTE4/LTB4- Inhibitors, 5-lipoxygenase inhibitors and PAF- receptor antagonists, (iii) Cox-2 inhibitors (iv) other MMP inhibitors,(v) interleukin-I inhibitors (vi) corticosteroids such as alclometasone, amcinonide, amelometasone, beclometasone, betamethasone, budesonide,

ciclesonide, clobetasol, cloticasone, cyclomethasone, deflazacort, deprodone, dexbudesonide, diflorasone, difluprednate, fluticasone, flunisolide, halometasone, halopredone, hydrocortisone, hydrocortisone, methylprednisolone, mometasone, prednicarbate, prednisolone, rimexolone, tixocortol, triamcinolone, ulobetasol, rofleponide, GW 215864, KSR 592, ST-126, dexamethasone and pharmaceutically acceptable salts, solvates thereof. Preferred corticosteroids include, for example, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, and dexamethasone;

2) Beta-agonists, experimental or commercial (i) suitable β2-agonists include, for example, one or more of albuterol, salbutamol, biltolterol, pirbuterol, levosalbutamol, tulobuterol, terbutaline, bambuterol, metaproterenol, fenoterol, salmeterol, carmoterol, arformoterol, formoterol, and their pharmaceutically acceptable salts or solvates thereofone or more β2- agonists may be chosen from those in the art or subsequently discovered. (ii) The β2-agonists may include one or more compounds described in, for example, U.S. Patent Nos. 3,705,233; 3,644,353; 3,642,896; 3,700,681; 4,579,985; 3,994,974; 3,937,838; 4,419,364; 5,126,375; 5,243,076; 4,992,474; and 4,011,258;

3) 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;

4) immunosuppressive agents, for example, cyclosporine, azathioprine and methotrexate, anti-inflammatory corticosteroids; and

5) anti-infective agents (e.g. antibiotics, antivirals).

DEFINITIONS

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. Alkyl groups can be optionally interrupted by atom(s) or group(s) independently selected from oxygen, sulfur, a phenylene, sulphinyl, sulphonyl group or $-NR_a-$, wherein R_a can be hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, $-C(=O)OR_\lambda$, SO_mR_ψ or

-C(=O)$NR_\lambda R_\pi$. This term can be exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-decyl, tetradecyl, and the like. Alkyl groups may be substituted further with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, oxo, thiocarbonyl, carboxy, carboxyalkyl, aryl, heterocyclyl, heteroaryl, (heterocyclyl)alkyl, cycloalkoxy, -CH=N-O(C_{1-6}alkyl), -CH=N-NH(C_{1-6}alkyl), -CH=N-NH(C_{1-6}alkyl)-C_{1-6}alkyl, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, aminocarbonylamino, -NHC(=O)R_λ, -$NR_\lambda R_\pi$, -C(=O)$NR_\lambda R_\pi$, -NHC(=O)$NR_\lambda R_\pi$, -C(=O)heteroaryl, C(=O)heterocyclyl, -O-C(=O)$NR_\lambda R_\pi$ {wherein R_λ and R_π are independently selected from hydrogen, halogen, hydroxy, alkyl, alkenyl, alkynyl, alkenyl, alkoxy, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or carboxy}, nitro or -SO_mR_ψ (wherein m is an integer from 0-2 and R_ψ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, alkyl substituents may be further substituted by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, -$NR_\lambda R_\pi$, -C(=O)$NR_\lambda R_\pi$, -OC(=O)$NR_\lambda R_\pi$,-NHC(=O)$NR_\lambda R_\pi$, hydroxy, alkoxy, halogen, CF_3, cyano, and -SO_mR_ψ; or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or -NR_α- (wherein R_α, R_λ, R_π, m and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, carboxyalkyl, -$NR_\lambda R_\pi$, -C(=O)$NR_\lambda R_\pi$, -O-C(=O)$NR_\lambda R_\pi$, hydroxy, alkoxy, halogen, CF_3, cyano, and -SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are the 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. Alkenyl groups can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and -NR_α- (wherein R_α is the same as defined earlier). 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,

alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, -$NHC(=O)R_\lambda$, -$NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -$NHC(=O)NR_\lambda R_\pi$, -$O\text{-}C(=O)NR_\lambda R_\pi$, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, keto, carboxyalkyl, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroaryl alkyl, aminosulfonyl, aminocarbonylamino, alkoxyamino, hydroxyamino, alkoxyamino, nitro or SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are as defined earlier). Unless otherwise constrained by the definition, alkenyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkoxy, halogen, -CF_3, cyano, -$NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -$O\text{-}C(=O)NR_\lambda R_\pi$ and -SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are as defined earlier). Groups, such as ethenyl or vinyl ($CH=CH_2$), 1-propylene or allyl ($-CH_2CH=CH_2$), iso-propylene (-$C(CH_3)=CH_2$), bicyclo[2.2.1]heptene, and the like, exemplify this term.

The term "alkynyl," unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, having from 2 to 20 carbon atoms. Alkynyl groups can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and -NR_α- (wherein R_α is the same as defined earlier). In the event that alkynyl groups are 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, keto, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, -$NHC(=O)R_\lambda$, -$NR_\lambda R_\pi$, -$NHC(=O)NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -$O\text{-}C(=O)NR_\lambda R_\pi$ or -SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, alkynyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3, -$NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -$NHC(=O)NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, cyano or -SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier).

The term "cycloalkyl," unless otherwise specified, refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which may optionally contain one or more olefinic bonds, unless otherwise constrained by the

definition. Such cycloalkyl groups can include, for example, single ring structures, including cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like or multiple ring structures, including adamantanyl, and bicyclo [2.2.1] heptane or cyclic alkyl groups to which is fused an aryl group, for example, indane, and the like. Spiro and fused ring structures can also be included. Cycloalkyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, $-NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-NHC(=O)R_\lambda$, $-C(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkoxy, halogen, CF_3, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-OC(=O)NR_\lambda R_\pi$, cyano or $-SO_mR_\psi$ (wherein R_λ, R_π, m and R_ψ are the 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 "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, propylphenyl, naphthylmethyl and the like.

The term "aryl," unless otherwise specified, refers to aromatic system having 6 to 14 carbon atoms, wherein the ring system can be mono-, bi- or tricyclic and are carbocyclic aromatic groups. For example, aryl groups include, but are not limited to, phenyl, biphenyl, anthryl or naphthyl ring and the like, optionally substituted with 1 to 3 substituents selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, CF_3, cyano, nitro, $COOR_\psi$, $NHC(=O)R_\lambda$, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$, $-SO_mR_\psi$, carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or amino carbonyl amino, mercapto, haloalkyl, optionally substituted aryl, optionally substituted heterocyclylalkyl, thioalkyl, $-CONHR_\pi$, $-OCOR_\pi$, $-COR_\pi$, $-NHSO_2R_\pi$ or $-SO_2NHR_\pi$ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier). Aryl groups optionally may be fused with a cycloalkyl group,

wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S. Groups such as phenyl, naphthyl, anthryl, biphenyl, and the like exemplify this term.

The term *"aryloxy"* denotes the group O-aryl wherein aryl is the same as defined above.

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms or a bicyclic or tricyclic 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), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy, aryl, alkoxy, aralkyl, cyano, nitro, heterocyclyl, heteroaryl, $-NR_\lambda R_\pi$, CH=NOH, $-(CH_2)_wC(=O)R_\eta$ {wherein w is an integer from 0-4 and R_η is hydrogen, hydroxy, OR_λ, $NR_\lambda R_\pi$, $-NHOR_\omega$ or -NHOH}, $-C(=O)NR_\lambda R_\pi$ $-NHC(=O)NR_\lambda R_\pi$, $-SO_mR_\psi$, $-O-C(=O)NR_\lambda R_\pi$, $-O-C(=O)R_\lambda$, or $-O-C(=O)OR_\lambda$ (wherein m, R_ψ, R_λ and R_π are as defined earlier and R_ω is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl). 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, furanyl, benzofuranyl, indolyl, benzthiazinyl, benzthiazinonyl, benzoxazinyl, benzoxazinonyl, quinazonyl, carbazolyl phenothiazinyl, phenoxazinyl, 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, wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, optionally substituted aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, -O-C(=O)Rλ, -O-C(=O)ORλ, -C(=O)NRλRπ, SOmRψ, -O-C(=O)NRλRπ, -NHC(=O)NRλRπ, -NRλRπ, mercapto, haloalkyl, thioalkyl, -COORψ, -COONHRλ, -CORλ, -NHSO2Rλ or SO2NHRλ (wherein m, Rψ, Rλ and Rπ are as defined earlier) or guanidine. Heterocyclyl can optionally include rings having one or

more double bonds. Such ring systems can be mono-, bi- or tricyclic. Carbonyl or sulfonyl group can replace carbon atom(s) of heterocyclyl. 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 benzotriazinone, isoindoledione, pyrimidinedione, aza-spiro[4.5]decanedione, benzo-oxazinedione, imidazolidinedione, phthalazinone,oxazolidinyl, tetrahydrofuranyl, dihydrofuranyl, benzoxazinyl, benzthiazinyl, imidazolyl, benzimidazolyl, tetrazolyl, carbaxolyl, indolyl, phenoxazinyl, phenothiazinyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, thiazolidinyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl, tetrahydropyranyl, piperazinyl, 3H-imidazo[4,5-b]pyridine, isoquinolinyl, 1H-pyrrolo[2,3-b]pyridine or piperazinyl and the like.

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

The term *"Heteroarylalkyl"* refers to heteroaryl group linked through alkyl portion, wherein the alkyl having 1 to 6 carbon atoms and heteroaryl are the same as defined earlier.

The term *"Heterocyclylalkyl"* refers to heterocyclyl group linked through alkyl portion, wherein the alkyl having 1 to 6 carbon atoms and heterocyclyl are the same as defined earlier.

The term *"amino"* refers to $-NH_2$

The term *"acyl"* refers to $-C(=O)R_4$ wherein R_4 is the same as defined earlier.

The term *"thioacyl"* refers to $-C(=S)R_4$ wherein R_4 is the same as defined above;

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

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.

Compounds described herein can contain one or more asymmetric carbon atoms and thus occur as diastereomers. These compounds can also exist as conformers/rotamers. All such isomeric forms of these compounds are included herein. 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.

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

The salt forms differ from the compound described herein in certain physical properties such as solubility, but the salts are otherwise equivalent for the purpose of this invention.

The term "*pharmaceutically acceptable solvates*" refers to solvates with water (i.e., hydrates) or pharmaceutically acceptable solvents, for example solvates with ethanol and the like. Such solvates are also encompassed within the scope of the disclosure. Furthermore, some of the crystalline forms for compounds described herein may exist as *polymorphs* and as such are intended to be included in the scope of the disclosure.

The term "polymorphs" includes all crystalline form as well as amorphous forms for compounds described herein and as such are included in the present invention.

The phrase "pharmaceutically acceptable carriers" is intended to include non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type.

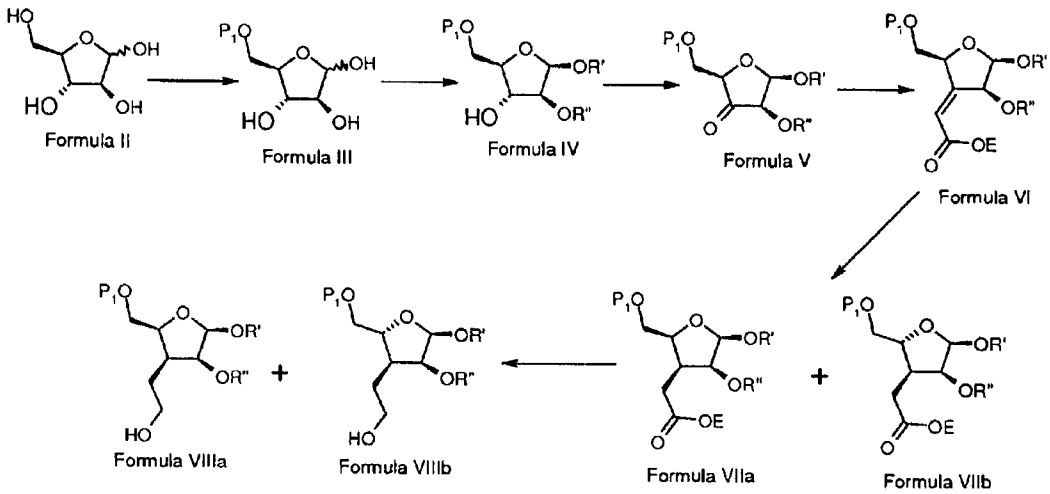
The term "pharmaceutically acceptable" means approved by regulatory agency of the federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans.

Examples of inflammatory conditions and autoimmune disorders in which the compounds of the invention have potentially beneficial effects in treatment methods may include, but are not limited to 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, psoriatic 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, inguinal hernia, retinal degeneration, diabetic retinopathy, macular degeneration, ocular inflammation, bone resorption 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, pancrealitis, hepatitis, endometriosis, pain, *e.g.*, that associated with inflammation and/or trauma, inflammatory diseases of the skin, *e.g.*, dermatitis, dermatosis, skin ulcers, psoriasis, eczema, systemic vasculitis, vascular dementia, thrombosis, atherosclerosis, restenosis, reperfusion injury, plaque calcification, myocarditis, aneurysm, stroke, pulmonary hypertension, left ventricular remodeling and heart failure. 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.

Compounds disclosed herein may be prepared, for example, by techniques well known in the organic synthesis and familiar to a practitioner ordinarily skilled in art of this invention. In addition, the processes described herein may enable the synthesis of the compounds of the present invention. However, these may not be the only means by which the compounds described in the invention may be synthesized. Further, the various synthetic steps described herein may be performed in alternate sequences in order to furnish the desired compounds.

Scheme-I



Compounds of Formulae VIIIa and VIIIb can be prepared by following, for example, synthetic routes as depicted in Scheme I. Thus, a compound of Formula II can be converted to a compound of Formula III (wherein P_1 is a silyl protecting group for example, *tert*-butyldimethyl silane, *tert*-butyldiphenylsilane or triisopropylsilane), which can then be converted to a compound of Formula IV (wherein P_1 is defined as above, R' and R" together form an acetal protecting group, for example, isopropylidene or cyclohexylidene acetal). The compound of Formula IV can be oxidized to form a compound of Formula V. The compound of Formula V can then be converted to a compound of Formula VI (wherein E is an alkyl group such as methyl, ethyl and the like), which can then be hydrogenated to form compounds of Formulae VIIa and VIIb. Compounds of Formulae VIIa and VIIb can be reduced to form compounds of Formulae VIIIa and VIIIb.

Silylation of a compound of Formula II to form a compound of Formula III can be carried out with silylating reagents such as, for example, tert-butyldimethylchlorosilane, triphenylchlorosilane, t-butyldiphenylchlorosilane in presence of a base, for example, imidazole or triethylamine in an organic solvent for example, dimethyl formamide, dimethylsulphoxide or acetonitrile.

Acetonation of a compound of Formula III to form a compound of Formula IV can be carried out with excess acetone as a solvent, in the presence of a mild acid catalyst, for

example, anhydrous copper (II) sulphate and camphorsulphonic acid, anhydrous zinc chloride and small amount of phosphoric acid, or anhydrous ferric chloride. Alternately, one may utilize trans-acetonation with dimethoxypropane in the presence of acid catalysts such as p-toluenesulfonic acid, sulfuric acid or montmorillonite-K.

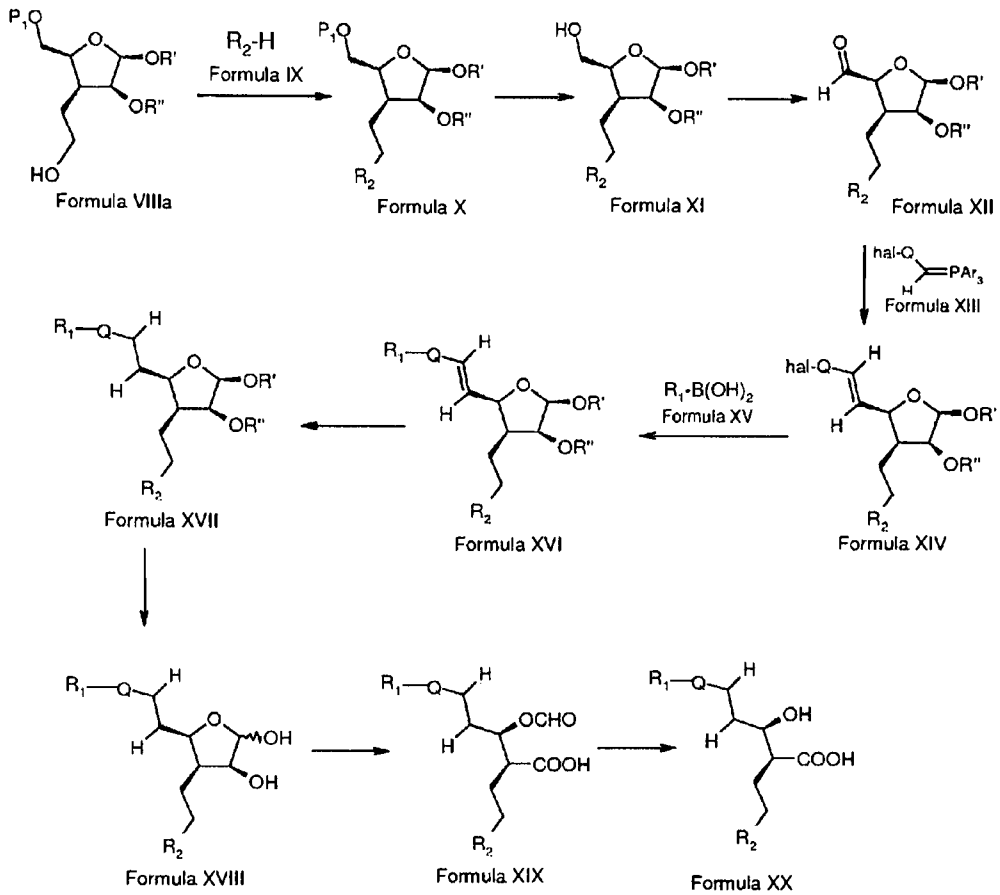
The compound of Formula IV can be oxidized to form a compound of Formula V, for example, by using Swern oxidation (Dimethylsulphoxide and oxalyl chloride) or Corey-Kim oxidation (N-chlorosuccinimide and Dimethylsulphide) in presence of a base, for example, triethylamine, diisopropylethylamine in a solvent, for example, dichloromethane or toluene. Alternatively, the compound of Formula IV can be oxidized to a compound of Formula V in, for example, dichloromethane or chloroform with an oxidizing agent, such as Dess-Martin reagent, pyridinium chlorochromate (PCC) or pyridinium dichromate (PDC). Oxidation of the compound of Formula IV to form a compound of Formula V can also be carried out catalytically using, for example, 2,2,6,6,-tetramethylpiperidine N-oxyl (TEMPO) and the 4-substituted derivatives thereof, including for example, 4-methoxy-TEMPO, 4-ethoxy-TEMPO, 4-acetoxy-TEMPO, 4-acetamino-TEMPO, 4-hydroxy-TEMPO, 4-benzoyloxy-TEMPO, 4-amino -TEMPO, N,N-dimethylamino-TEMPO, or 4-oxo-TEMPO as a catalyst, in the presence of a co-catalyst, for example, potassium bromide or sodium bromide, with an oxidant, for example, sodium hypochlorite, potassium hypochlorite, calcium hypochlorite, sodium hypobromite or potassium hypobromite in a solvent, for example, methylene chloride, chloroform, ethyl acetate, butyl acetate, acetonitrile, tetrahydrofuran, toluene, acetone, diethyl ether, methyl tert-butyl ether, pentane, hexane or mixtures of such solvents.

The compound of Formula V can be converted to a compound of Formula VI, for example, via a Horner-Wadsworth-Emmons reaction, thus a compound of Formula V can be reacted with phosphonate carbanions (produced *in situ* by treating trimethylphosphonoacetate or triethylphosphonoacetate with a base, for example, sodium hydride, potassium hydride, potassium tert-butoxide, sodium tert-butoxide, potassium carbonate, triethylamine in an organic solvent, for example, tetrahydrofuran or dimethoxyethane to give a compound of Formula VI. Alternately, the Wittig reaction can be carried out using the preformed Wittig reagent such as (carboethoxymethylene)-triphenylphosphorane.

Hydrogenation of a compound of Formula VI to form compounds of Formulae VIIa and VIIb can be carried with palladium on carbon in presence of hydrogen, in a suitable solvent, for example, methanol, ethanol, propanol, tetrahydrofuran, ethyl acetate or mixture(s) thereof.

Compounds of Formulae VIIa and VIIb can be reduced to give compounds of Formula VIIIa and VIIIb in the presence of a reducing agent, for example, lithium aluminium hydride, lithium triethyl borohydride or sodium borohydride, in the presence of an additive, for example, lithium chloride or aluminium chloride, in an organic solvent, for example, tetrahydrofuran, diethylether or diglyme.

Scheme-II



Compounds of Formula XX can be prepared, for example, by following synthetic routes as depicted in Scheme II. Thus, a compound of Formula VIIIa (wherein P_1, R' and R'' are same as defined earlier), can react with a compound of Formula IX (wherein R_2 is

an N-containing heterocyclyl or heteroaryl) to give a compound of Formula X. The compound of Formula X can undergo deprotection to form a compound of Formula XI which on oxidation can give a compounds of Formula XII. The compound of Formula XII on reaction with a compound of Formula XIII (wherein Q is same as defined earlier, hal is Cl, Br or I and Ar is phenyl) can form a compound of Formula XIV. The compound of Formula XIV can then react with a compound of Formula XV (wherein R_1 is same as defined earlier) to form a compound of Formula XVI which can then be hydrogenated to form a compound of Formula XVII. The compound of Formula XVII can undergo deprotection to form a compound of Formula XVIII which can then be oxidatively cleaved to form a compound of Formula XIX. The compound of Formula XIX can be deformylated to form a compound of Formula XX.

The reaction of a compound of Formula VIIIa with a compound of Formula IX to give a compound of Formula X can be carried out using triphenylphosphine or tributylphosphine and diethyl azodicarboxylate, diisoproyl azodicarboxylate or 1,1'-azodicarbonyldipiperidine in an organic solvent, for example, tetrahydrofuran, dimethylformamide or toluene.

The compound of Formula X can be deprotected to form a compound of Formula XI with deprotecting agents, for example, tetrabutylammonium fluoride or potassium fluoride in an organic solvent, for example, tetrahydrofuran, dimethylformamide, diethyl ether or dioxane, optionally in the presence of crown ethers such as, for example, 18-crown-6. The oxidation of a compound of Formula XI to give a compound of Formula XII can be carried out similarly as that of conversion of a compound of Formula IV to form a compound of Formula V.

The compound of Formula XII can be converted to a compound of Formula XIV by reacting with a compound of Formula XIII (Wittig reagent, *i.e.*, an ylide, prepared by reacting a phosphonium salt, in turn prepared from triphenylphophine and alkyl halide, in a solvent for example, tetrahydrofuran, dimethyl sulphoxide or diethyl ether, with a strong base, for example, n-butyllithium, sodium hydride or potassium tert-butoxide).

The reaction of a compound of Formula XIV with a compound of Formula XV can be carried out in the presence of a metal catalyst, for example, 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 for example, potassium carbonate or cesium carbonate, in an organic solvent, for example, toluene, dimethyl sulphoxide, dimethylformamide, tetrahydrofuran, dioxane or diethyl ether.

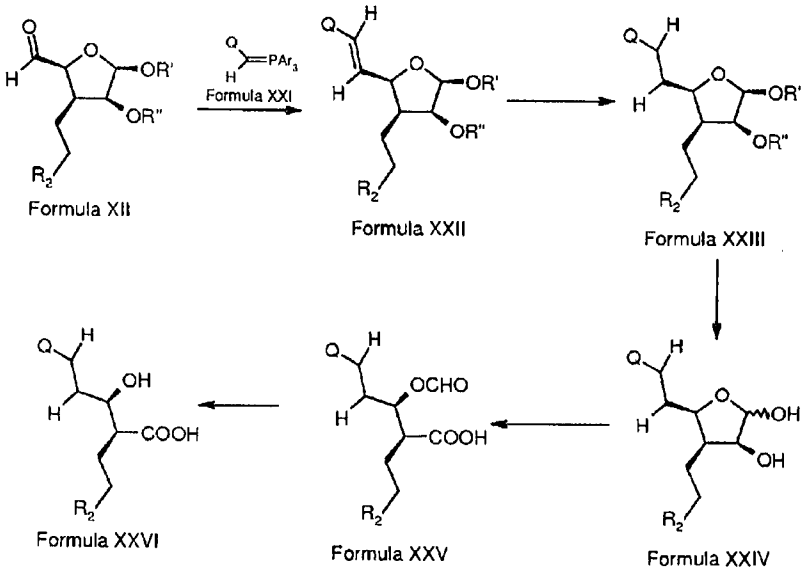
Hydrogenation of a compound of Formula XVI to form a compound of Formula XVII can be carried out similarly as conversion of a compound of Formula VI to compounds of Formulae VIIa and VIIb.

The compound of Formula XVII can be deprotected to form a compound of Formula XVIII with perchloric acid, acetic acid or hydrochloric acid in solvent(s), for example, acetonitrile, water, tetrahydrofuran or mixture(s) thereof.

Conversion of a compound of Formula XVIII to form a compound of Formula XIX can be carried out by diol cleavage in presence of, for example, sodium metaperiodate, lead tetraacetate, pyridinium chlorochromate or manganese dioxide, in co-solvents, for example, tert-butanol-water, methanol-tetrahydrofuran or tert-butanol-tetrahydrofuran, followed by oxidation with, for example, potassium permangnate or with a mixture of sodium dihydrogen phosphate, sodium chlorite and hydrogen peroxide.

The compound of Formula XIX can be deformylated to form a compound of Formula XX in presence of a base for example, potassium carbonate, sodium carbonate or triethylamine in a solvent, for example, methanol, tetrahydrofuran or mixture(s) thereof.

Scheme-III



Compounds of Formula XXVI can be prepared by following synthetic routes, for example, as depicted in Scheme III. Thus, a compound of Formula XII can react with a compound of Formula XXI (wherein Q is same as defined earlier and Ar is phenyl) to form a compound of Formula XXII (wherein R_2 is an N-containing heterocyclyl or heteroaryl), which can further be hydrogenated to form a compound of Formula XXIII. The compound of Formula XXIII can be deprotected to form a compound of Formula XXIV, which can then be oxidatively cleaved to give a compound of Formula XXV. The compound of Formula XXV can then be deformylated to form a compound of Formula XXVI.

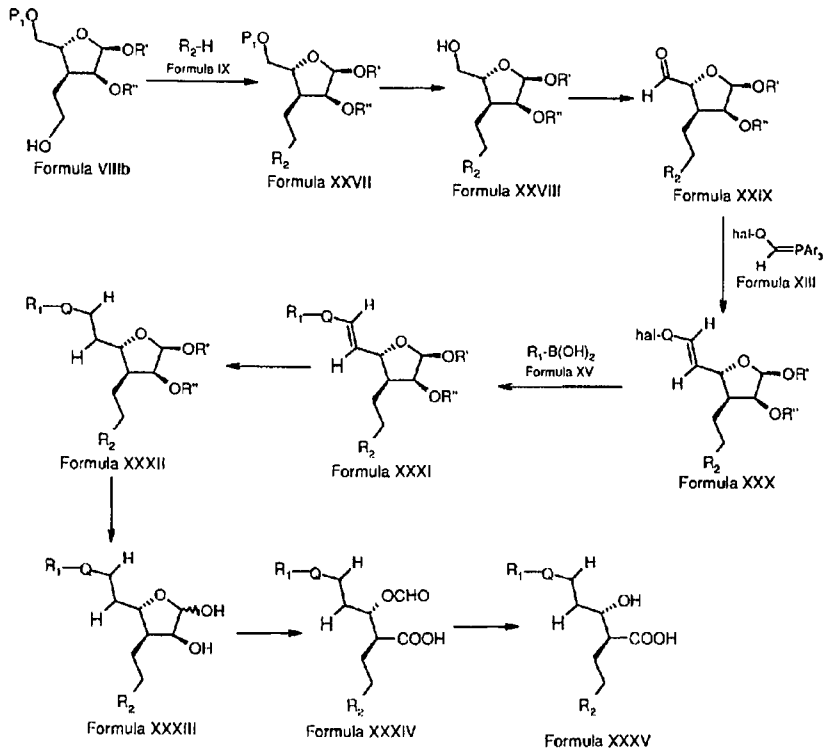
The reaction of a compound of Formula XII with a compound of Formula XXI to form a compound of Formula XXII can be carried out similarly as conversion of a compound of Formula XII to a compound of Formula XIV. Hydrogenation of a compound of Formula XXII to give a compound of Formula XXIII can be carried out under similar conditions as that of conversion of a compound of Formula VI to compounds of Formulae VIIa and VIIb.

Deprotection of a compound of Formula XXIII to give a compound of Formula XXIV can be carried out similarly as conversion of a compound of Formula XVII to a compound of Formula XVIII. The oxidative cleavage of a compound of Formula XXIV to

form a compound of Formula XXV can be carried out under similar condition as that of conversion of a compound of Formula XVIII to a compound of Formula XIX.

Deformylation of a compound of Formula XXV to form a compound of Formula XXVI can be carried out similarly as conversion of a compound of Formula XIX to give a compound of Formula XX.

Scheme-IV



Compounds of Formula XXXV can be prepared by, for example, following synthetic routes as depicted in Scheme IV. Thus, a compound of Formula VIIIb (wherein P_1, R' and R'' are same as defined earlier), can react with a compound of Formula IX (wherein R_2 is an N-containing heterocyclyl or heteroaryl to give a compound of Formula XXVII. The compound of Formula XXVII can be deprotected to form a compound of Formula XXVIII, which on oxidation can give a compound of Formula XXIX. The compound of Formula XXIX on reaction with a compound of Formula XIII can form a compound of Formula XXX which can then react with a compound of Formula XV (wherein R_1 is same as defined earlier) to form a compound of Formula XXXI. The compound of Formula XXXI can then be hydrogenated to form a compound of Formula XXXII which can then undergo deprotection to form a compound of

Formula XXXIII. The compound of Formula XXXIII can be oxidatively cleaved to form a compound of Formula XXXIV. The compound of Formula XXXIV can then be deformylated to form a compound of Formula XXXV.

The reaction of a compound of Formula VIIIb with a compound of Formula IX to give a compound of Formula XXVII can be carried out similarly as that of conversion of a compound of Formula VIIIa to form a compound of Formula X.

Deprotection of a compound of Formula XXVII to give a compound of Formula XXVIII can be carried out similarly as that of deprotection of a compound of Formula X to form a compound of Formula XI.

Oxidation of a compound of Formula XXVIII to give a compound of Formula XXIX can be carried out similarly as that of conversion of a compound of Formula IV to form a compound of Formula V.

The reaction of a compound of Formula XXIX with a compound of Formula XIII to form a compound of Formula XXX can be carried out under similar condition as that of conversion of a compound of Formula XII to form a compound of Formula XIV.

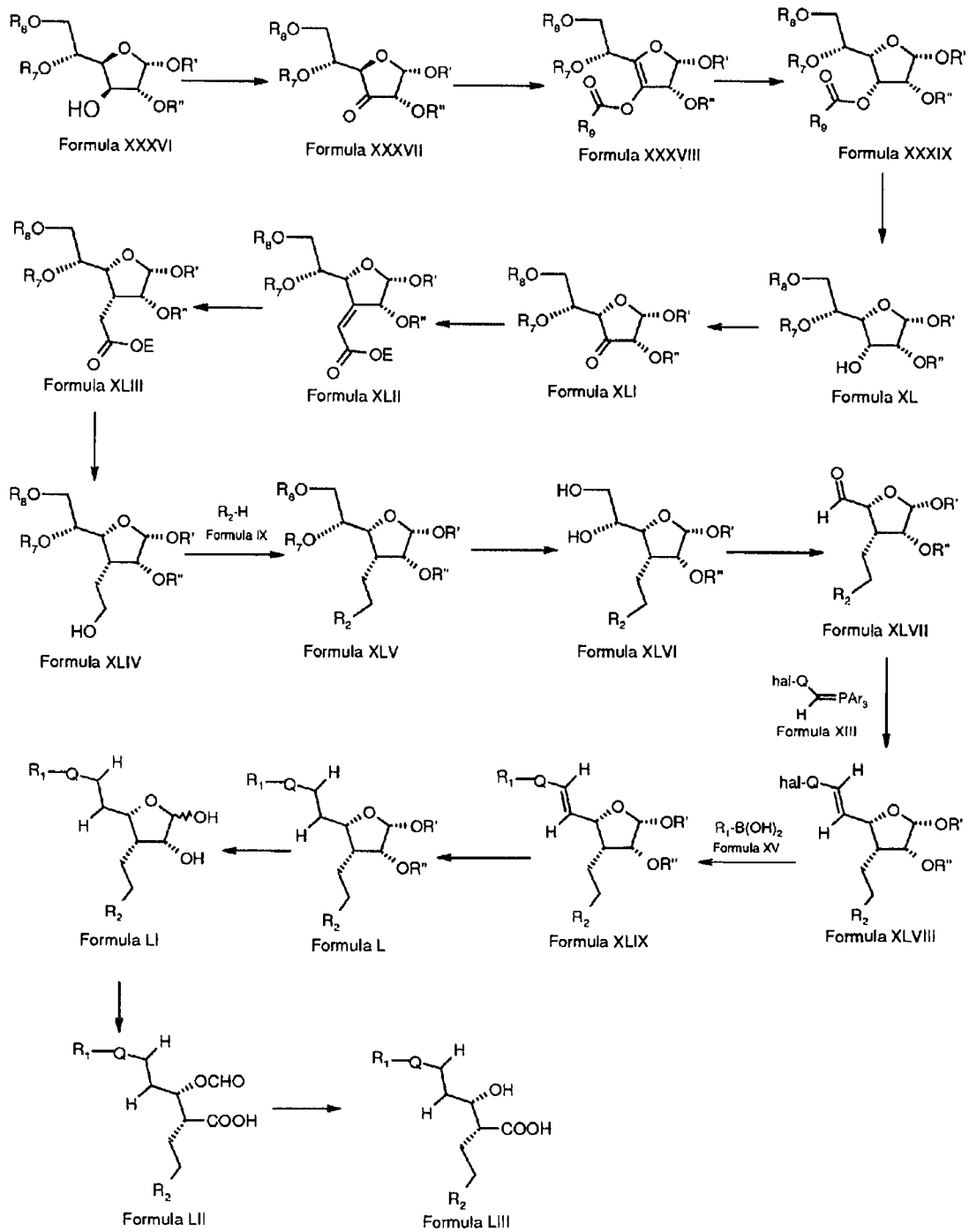
Coupling of a compound of Formula XXX with a compound of Formula XV to form a compound of Formula XXXI can be carried out similarly as conversion of a compound of Formula XIV to form a compound of Formula XVI.

Hydrogenation of a compound of Formula XXXI to form a compound of Formula XXXII can be carried out similarly as conversion of a compound of Formula VI to form compound of Formulae VIIa and VIIb. The compound of Formula XXXII can be deprotected to form a compound of Formula XXXIII under similar condition as that of conversion of a compound of Formula XVII to form a compound of Formula XVIII.

Oxidative cleavage of a compound of Formula XXXIII to form a compound of Formula XXXIV can be carried out similarly as conversion of a compound of Formula XVIII to give a compound of Formula XIX.

Deformylation of a compound of Formula XXXIV to form a compound of Formula XXXV can be carried out under similar condition as that of conversion of a compound of Formula XIX to form a compound of Formula XX.

Scheme-V



Compounds of Formula LIII can be prepared, for example, by following synthetic routes as depicted in Scheme V. Thus, a compound of Formula XXXVI (wherein R_7 and

R_8 together form a acetal protecting group, for example, isopropylidene acetal, R' and R" are same as described earlier) can be oxidized to form a compound of Formula XXXVII which can then be converted to form a compound of Formula XXXVIII (wherein R_9 is alkyl or aryl). The compound of Formula XXXVIII can be hydrogenated to give a compound of Formula XXXIX which can then be hydrolyzed to give a compound of Formula XL. The compound of Formula XL can be oxidized to give a compound of Formula XLI which can then be converted to form a compound of Formula XLII. The compound of Formula XLII can be hydrogenated to form a compound of Formula XLIII which can then be reduced to form a compound of Formula XLIV. The compound of Formula XLIV can then be reacted with a compound of Formula IX (wherein R_2 is an N-containing heterocyclyl or heteroaryl) to afford a compound of Formula XLV which can then be deprotected to form a compound of Formula XLVI. The compound of Formula XLVI can be oxidized to form a compound of Formula XLVII which can then react with a compound of Formula XIII to form a compound of Formula XLVIII. The compound of Formula XLVIII can then be reacted with a compound of Formula XV (wherein R_1 is same as defined earlier) to give a compound of Formula XLIX which can then be hydrogenated to form a compound of Formula L. The compound of Formula L is deprotected to form a compound of Formula LI which can then be oxidatively cleaved to form a compound of Formula LII. The compound of Formula LII is then deformylated to form a compound of Formula LIII.

Oxidation of a compound of Formula XXXVI to form a compound of Formula XXXVII can be carried out under similar condition as that of oxidation of a compound of Formula IV to form a compound of Formula V. The compound of Formula XXXVII can be converted to a compound of Formula XXXVIII in presence of, for example, acetic anhydride or benzoic anhydride in presence of base, such as for example, pyridine, triethylamine or morpholine.

The compound of Formula XXXVIII can be hydrogenated to form a compound of Formula XXXIX similarly as that of hydrogenation of a compound of Formula VI to give compounds of Formulae VIIa and VIIb. The hydrolysis of a compound of Formula XXXIX to form a compound of Formula XL can be carried out with a base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate or sodium methoxide in the presence of a solvent, for example, methanol, ethanol or

isopropanol. The compound of Formula XL can be oxidized to form a compound of Formula XLI similarly as that of conversion of a compound of Formula IV to form a compound of Formula V.

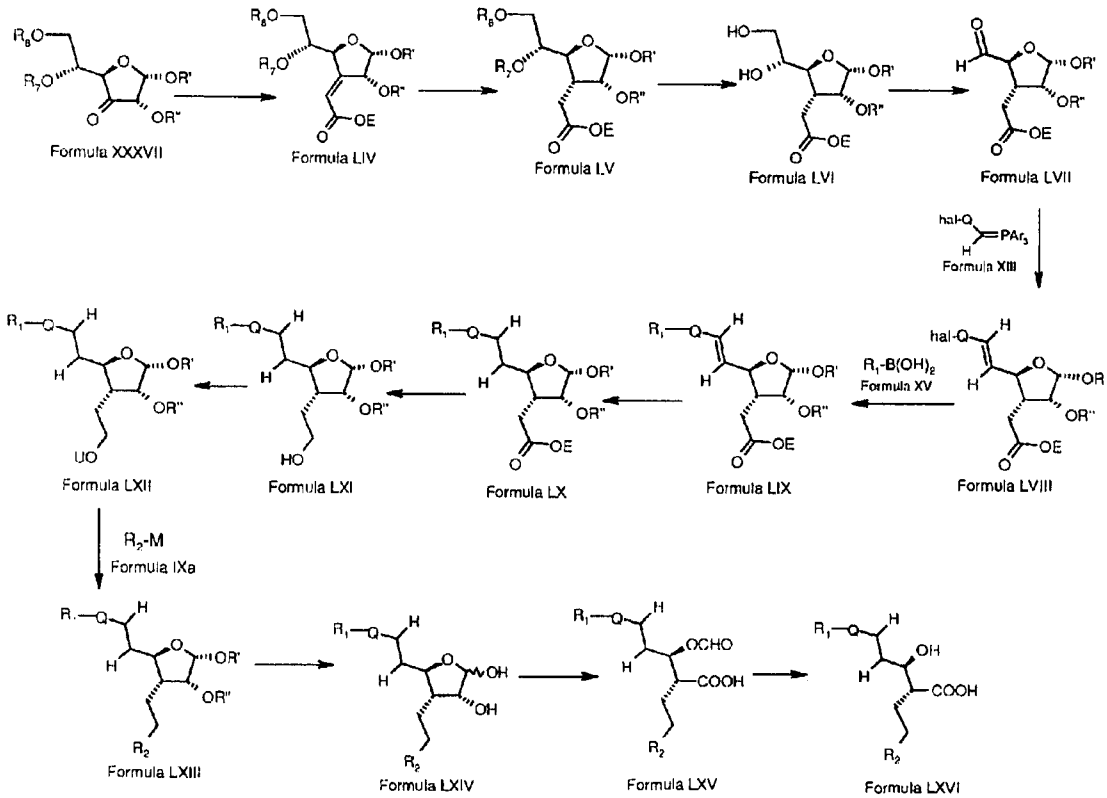
Conversion of a compound of Formula XLI to form a compound of Formula XLII can be carried out under similar condition as that of conversion of a compound of Formula V to form a compound of Formula VI. The compound of Formula XLII can be hydrogenated to form a compound of Formula XLIII similarly as that of conversion of compound of Formula VI to compounds of Formulae VIIa and VIIb. The reduction of a compound of Formula XLIII to form a compound of Formula XLIV can be carried out under similar condition as that of reduction of compounds of Formulae VIIa and VIIb to form compounds of Formulae VIIIa and VIIIb. The reaction of a compound of Formula XLIV with a compound of Formula IX to form compound of Formula XLV can be carried out similarly as that of conversion of a compound of Formula VIIIa to form a compound of Formula X.

Selective acetonide deprotection of a compound of Formula XLV to form a compound of Formula XLVI can be carried out with perchloric acid in a solvent, for example, tetrahydrofuran or diethyl ether or trifluoroacetic acid in dichloromethane. Oxidation of a compound of Formula XLVI to form a compound of Formula XLVII can be carried out with, for example, sodium metaperiodate, lead tetraacetate, pyridinium chlorochromate or manganese dioxide in a solvent, for example, acetone, methanol, ethanol or tert-butanol.

The reaction of a compound of Formula XLVII with a compound of Formula XIII to form a compound of Formula XLVIII can be carried out similarly as that of conversion of compound of Formula XII to form a compound of Formula XIV. Coupling of a compound of Formula XLVIII with a compound of Formula XV to form a compound of Formula XLIX can be carried out similarly as conversion of a compound of Formula XIV to form a compound of Formula XVI. The compound of Formula XLIX can be hydrogenated to form a compound of Formula L under similar condition as that of conversion of compound of Formula VI to compound of Formulae VIIa and VIIb. Deprotection of a compound of Formula L to give a compound of Formula LI can be carried out under similar condition as that of conversion of a compound of Formula XVII to form a compound of Formula XVIII.

The oxidative cleavage of a compound of Formula LI to form a compound of Formula LII can be done similarly as that of conversion of a compound of Formula XVIII to form a compound of Formula XIX. The compound of Formula LII can be deformylated to a compound of Formula LIII under similar condition as that of conversion of compound of Formula XIX to form compound of Formula XX.

Scheme-VI



Compounds of Formula LXVI can be prepared, for example, by following synthetic routes as depicted in Scheme VI. Thus, a compound of Formula XXXVII (wherein R_7, R_8, R' and R" are same as described earlier) can be converted to form a compound of Formula LIV which can then be hydrogenated to form a compound of Formula LV. The compound of Formula LV can be selectively deprotected to form a compound of Formula LVI which on oxidation, can form a compound of Formula LVII. The compound of Formula LVII can be reacted with a compound of Formula XIII to form a compound of Formula LVIII which can then be coupled with a compound of Formula XV (wherein R_1 is same as defined earlier) to give a compound of Formula LIX. The

compound of Formula LIX can be hydrogenated to form a compound of Formula LX which can then be reduced to form a compound of Formula LXI. The compound of Formula LXI can be activated to form a compound of Formula LXII (wherein U is an O-activating group, for example, mesyl, tosyl or triflate), which can then be reacted with a compound of Formula IXa (wherein R_2 is an N-containing heterocyclyl or heteroaryl and M is a metal, for example, potassium, lithium or sodium) to form a compound of Formula LXIII. The compound of Formula LXIII can then be deprotected to form a compound of Formula LXIV which can be oxidatively cleaved to form a compound of Formula LXV. The compound of Formula LXV can be deformylated to form a compound of Formula LXVI.

The compound of Formula XXXVII can be converted to form a compound of Formula LIV under similar condition as that of conversion of a compound of Formula V to form a compound of Formula VI. Hydrogenation of a compound of Formula LIV to form a compound of Formula LV can be carried out similarly as that of conversion of a compound of Formula VI to form compounds of Formulae VIIa and VIIb.

The compound of Formula LV can be selectively deprotected to form a compound of Formula LVI under similar conditions as that of conversion of a compound of Formula XLV to give a compound of Formula XLVI. The compound of Formula LVI can be oxidized to form a compound of Formula LVII similarly as that of conversion of a compound of Formula XLVI to form a compound of Formula XLVII.

The reaction of a compound of Formula LVII with a compound of Formula XIII to form a compound of Formula LVIII can be carried out under similar conditions as that of conversion of a compound of Formula XII to form a compound of Formula XIV. The compound of Formula LVIII can be coupled with a compound of Formula XV to give a compound of Formula LIX under similar condition as that of conversion of a compound of Formula XIV to form a compound of Formula XVI. Hydrogenation of a compound of Formula LIX to form a compound of Formula LX can be carried out under similar condition as that of conversion of a compound of Formula VI to form compounds of Formulae VIIa and VIIb.

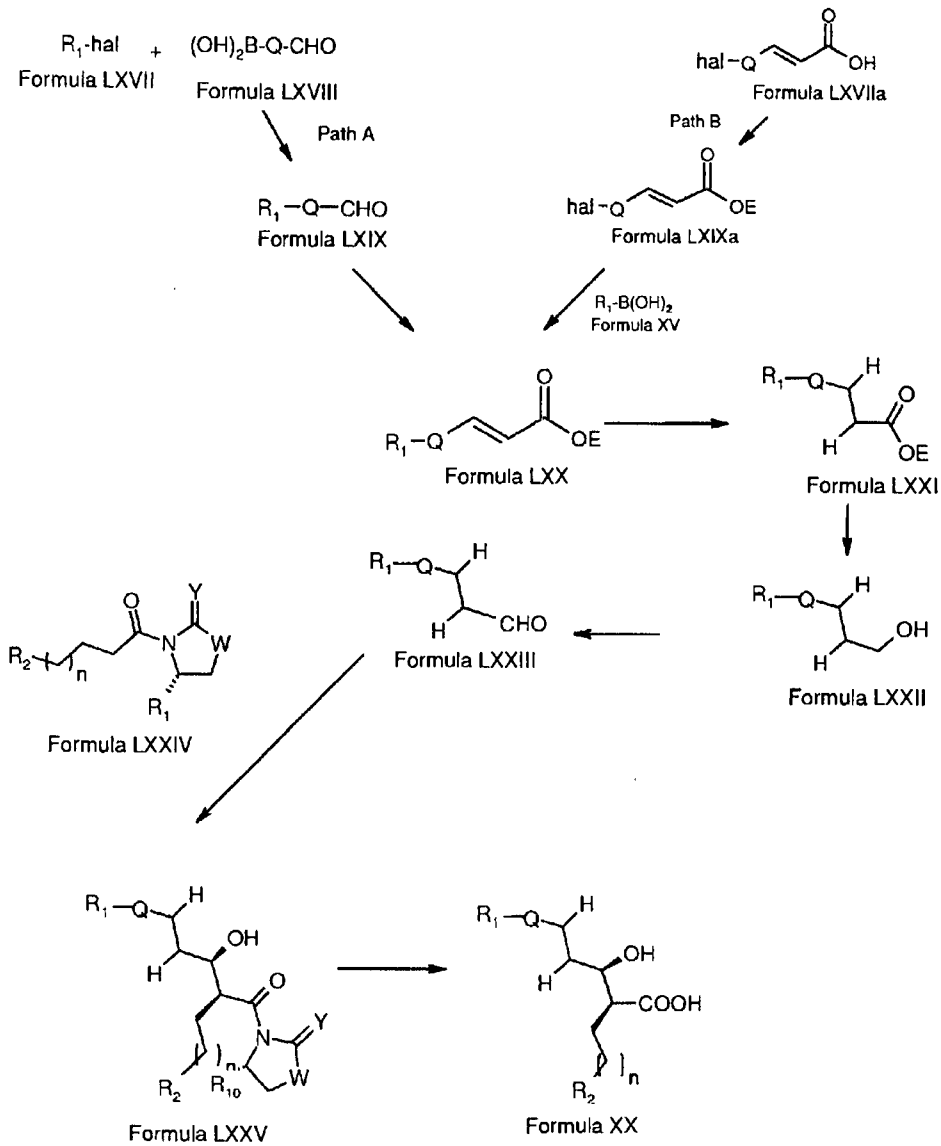
The compound of Formula LX can be reduced to form a compound of Formula LXI under similar condition as that of conversion of compound of Formulae VIIa and VIIb to form compounds of Formulae VIIIa and VIIIb.

A compound of Formula LXI can be activated to form a compound of Formula LXII in a solvent, for example, dichloromethane, toluene or dichloroethane, using a base, for example, triethylamine, diisopropylamine or N-methylmorpholine, using a suitable sulphonyl chloride, for example, methanesulphonyl chloride or p-toluene sulphonyl chloride. The reaction of a compound of Formula LXII with a compound of Formula IXa to yield a compound of Formula LXIII can be carried out in an organic solvent, for example, tetrahydrofuran, dimethyl sulphoxide, dimethylformamide, acetonitrile, dioxane, dimethylacetamide. Alternatively, the reaction of a compound of Formula LXII with a compound of Formula IX to yield a compound of Formula LXIII 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, or dimethylacetamide. Alternatively, a compound of Formula LXI can be converted to a compound of Formula LXIII following similar protocols as that of the reaction of a compound of Formula VIIIa with a compound of Formula IX to give a compound of Formula X.

The compound of Formula LXIII can be deprotected to form a compound of Formula LXIV similarly as that of conversion of a compound of Formula XVII to form a compound of Formula XVIII.

The oxidative cleavage of a compound of Formula LXIV to give a compound of Formula LXV can be done similarly as that of conversion of a compound of Formula XVIII to form a compound of Formula XIX. The compound of Formula LXV can be deformylated to form a compound of Formula LXVI under similar condition as that of conversion of a compound of Formula XIX to form a compound of Formula XX.

Scheme-VII



Compounds of Formula XX can also be prepared, for example, by following alternate synthetic routes as depicted in Scheme VII. Thus, a compound of Formula LXVII can be coupled with a compound of Formula LXVIII to form a compound of Formula LXIX (wherein R_1 and Q are same as defined earlier), which can then be converted to a compound of Formula LXX (Path A)(wherein E is same as defined earlier). Alternately, compound of Formula LXVIIIa can undergo esterification to gives a compound of Formula LXIXa, which can be coupled with compound of Formula XV to

form compound of Formula LXX (PathB) (wherein E is same as defined earlier). The compound of Formula LXX can be hydrogenated to form compound of Formula LXXI, which can then be reduced to form a compound of Formula LXXII. The compound of Formula LXXII can be oxidized to form a compound of Formula LXXIII, which can then react with a compound of Formula LXXIV (wherein, when R_2 is N-containing heterocyclyl or heteroaryl, Y and W can be oxygen or sulphur, R_{10} can be alkyl, aryl or aralkyl and n is as defined earlier) to form compound of Formula LXXV. The compound of Formula LXXII can be further hydrolysed to form a compound of Formula XX.

Coupling of a compound of Formula LXVII with a compound of Formula LXVIII to form a compound of Formula LXIX can be carried out similarly as conversion of a compound of Formula XIV to form a compound of Formula XVI.

Conversion of a compound of Formula LXIX to form a compound of Formula LXX can be carried out under similar condition as that of conversion of a compound of Formula V to form a compound of Formula VI. Esterification of compound of Formula LXVIIIa to gives a compound of Formula LXIXa can be carried out in a solvent, for example, methanol, ethanol, tert-butanol or benzyl alcohol with a halogenating agent, for example, thionyl chloride or oxalyl chloride. Coupling of a compound of Formula LXIXa with a compound of Formula XV to form a compound of Formula LXX can be carried out similarly as conversion of a compound of Formula XIV to form a compound of Formula XVI.

The compound of Formula LXX can be hydrogenated to form a compound of Formula LXXI similarly as that of conversion of compound of Formula VI to compounds of Formulae VIIa and VIIb. The reduction of a compound of Formula LXXI to form a compound of Formula LXXII can be carried out under similar condition as that of reduction of compounds of Formulae VIIa and VIIb to form compounds of Formulae VIIIa and VIIIb. The compound of Formula LXXII can be oxidized to form a compound of Formula LXXIII similarly as that of oxidation of a compound of Formula IV to form a compound of Formula V.

The asymmetric aldol addition of a compound of Formula LXXIII with a compound of Formula LXXIV to form compound of Formula LXXIV can be carried out by generating the enolates with titanium chloride, dibutyl boron triflate, dialkyl boron

chloride or tin(II) triflate, in the presence of a base, for example, diisopropylethylamine, tetramethylethelenediamine, tributylamine, N-ethylpiperidine, 1,4-diazabicyclo[2.2.2]octane, 1,8-Diazabicyclo[5.4.0]undec-7-ene, tetramethylpropylenediamine, or (-) sparteine, in a solvent, for example, dichloromethane, or diethyl ether.

Hydrolysis of a compound of Formula LXXIV to form a compound of Formula XX can be carried out with hydrogen peroxide and lithium hydroxide, in the presence of a solvent, for example, tetrahydrofuran, water or mixture(s) thereof.

Compound Nos. 1 to 81, 86-88, 90-95, 97-119, 121-142, 144-203, 211-213 and 226-232 were prepared following Schemes I and II. Compound Nos. 82 to 85, and 204 were prepared following Schemes I, II and III. Compound Nos. 143, and 208 were prepared following Scheme IV. Compound Nos. 120, and 205-207 were prepared following Scheme V. Compound Nos. 89, and 96 were prepared following Scheme VI. Compound Nos. 86, 209-210 and 214-225 were prepared following Scheme VII.

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

The following examples are set forth to demonstrate general synthetic procedures for the preparation of representative compounds of the present invention. The examples are provided to illustrate particular aspect of the disclosure and do not limit the scope of the present invention.

EXAMPLES

Synthesis of starting materials:

Synthesis of 6-methyl-1,2,3-benzotriazin-4(3*H*)-one

The title compound was prepared following the procedure outlined in *J. Med. Chem.*, (1992), 35(14), 2626-2630.

The following analogues of 6-methyl-1,2,3-benzotriazin-4(3H)-one were prepared analogously,

8-methyl-1,2,3-benzotriazin-4(3H)-one;

7-methyl-1,2,3-benzotriazin-4(3H)-one;

6-methyl-1,2,3-benzotriazin-4(3H)-one;

8-methoxy-1,2,3-benzotriazin-4(3H)-one;

6-methoxy-1,2,3-benzotriazin-4(3H)-one;

8-chloro-1,2,3-benzotriazin-4(3H)-one;

7-chloro-1,2,3-benzotriazin-4(3H)-one;

6-chloro-1,2,3-benzotriazin-4(3H)-one;

5-chloro-1,2,3-benzotriazin-4(3H)-one;

6,7-difluoro-1,2,3-benzotriazin-4(3H)-one;

8-fluoro-1,2,3-benzotriazin-4(3H)-one;

5-fluoro-1,2,3-benzotriazin-4(3H)-one;

6-fluoro-1,2,3-benzotriazin-4(3H)-one;

5-(6-methoxypyridin-3-yl)-1,2,3-benzotriazin-4(3H)-one;

7-(6-methoxypyridin-3-yl)-1,2,3-benzotriazin-4(3H)-one; and

7-(trifluoromethyl)-1,2,3-benzotriazin-4(3H)-one.

Synthesis of 5-tert-butyl-1H-isoindole-1,3(2H)-dione

The title compound was prepared following the procedure outlined in *Chem. Ber.*, (1877), 10, 1163.

Mass (m/z): 204.12(M^+ +1)

The following analogues of 5-tert-butyl-1H-isoindole-1,3(2H)-dione were prepared analogously:

4-fluoro-1H-isoindole-1,3(2H)-dione; and

5-chloro-1H-isoindole-1,3(2H)-dione.

Synthesis of (4-bromobenzyl)(triphenyl)phosphonium bromide

A mixture of 1-bromo-4-(bromomethyl)benzene (5g) and triphenylphosphine(5.24 g) in xylene (20 mL) were heated to reflux for 18 hours. The reaction mixture was cooled, filtered, washed with hexane and tried under vacuum to afford the title compound (8 g).

Mass (m/z):433.9 (M^+ +1)

The following Wittig salts were prepared analogously:

[(4-bromo-2-thienyl)methyl]triphenyl phosphonium bromide;

[(6-bromopyridin-3-yl)methyl](triphenyl)phosphonium bromide;

(4-bromo-2-fluorobenzyl)(triphenyl)phosphonium bromide;

4-tert-butylbenzyl)(triphenyl)phosphonium bromide;

triphenyl[4-(trifluoromethyl)benzyl]phosphonium bromide;

benzyl(triphenyl)phosphonium bromide;

(4-bromo-3-fluorobenzyl)(triphenyl)phosphonium bromide;

(4-bromo-2-fluorobenzyl)(triphenyl)phosphonium bromide; and

(4-chloro-3-fluorobenzyl)(triphenyl)phosphonium bromide.

Synthesis of 4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid

Step a: Synthesis of ethyl 4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoate

In a dry round botton flask, 1,2,3-benzotriazin-4(3*H*)-one (50 g), ethyl 4-bromobutanoate

(86.2 g) and potassium carbonate (141 g) were taken and dissolved in dimethylformamide (350 mL) and heated to 60-70 ℃ for 3-4 hours. After cooling to room temperature, water was added to the reaction mixture and extracted with ethyl acetate. The combined organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Solvents were evaporated under reduced pressure and the crude product was purified by silica gel flash column chromatography over silica gel using 20% ethylacetate in hexane as eluant to afford the title compound (68 g).

Step b: Synthesis of 4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid

To a stirred solution compound (40 g), obtained from step a above, in a solvent mixture of tetrahydrofuran/methanol.water (3:1:1, 400 mL) was added lithium hydroxide monohydrate (6.43 g) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C until completion of hydrolysis. The solvents were evaporated, diluted with water and extracted with ethyl acetate. The aqueous layers were acidified with saturated aqueous sodium hydrogen sulfate solution and extracted with ethyl acetate. The combined layers were washed with water, brine and dried over anhydrous sodium sulfate. The solvents were evaporated under reduced pressure to afford the title compound (28 g).

The following analogue of 4-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)butanoic acid was prepared analogously:

3-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)propanoic acid

Synthesis of 3-{4-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-4-oxobutyl}-1,2,3-benzotriazin-4(3*H*)-one

Step a: Synthesis of (2S)-2-amino-3-phenylpropan-1-ol

(**Ref:** *J. Org. Chem.* **1993,** *58,* 3568-3571)

To a suspension of sodium borohydride (16.5 g) in dry tetrahydrofuran (600 mL), (L)-phenylalanine (30g) was added at one portion. The flask was cooled to 0 °C under nitrogen atmosphere. Iodine (46.18 g) solution in tetrahydrofuran (150 mL) was added slowly in dropwise manner over 40 minutes, resulting in vigorous evolution of H_2. After complete addition of iodine, the reaction mixture was heated to reflux for 18 hours and cooled to room temperature. The reaction mixture was quenched with methanol until the reaction mixture become clear. Further, the solution was stirred for 30 minutes at room temperature. The solvents were removed by rotary evaporation to obtain a white paste which was dissolved by 20% aqueous potassium hydroxide (450 mL). The solution was stirred for 4 hours and then dichloromethane was added. The organic layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvents were evaporated under reduced pressure to afford 32.5 g of (L)-phenylalaninol as a viscous liquid. The crude product was used as such for the next step.

Step b: Synthesis of (4S)-4-benzyl-1,3-thiazolidine-2-thione

(**Ref:** *J. Org. Chem.* **1995, *60,*** 6604-6607)

To a solution of compound (32.5 g) obtained in stepa above,in 1N aqueous potassium hydroxide (1 lit), carbon disulphide(68 mL, 5.0 equiv.) was added and the reaction mixture was refluxed for 16 hours. After cooling to room temperature, the aqueous solution was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using 15% ethyl acetate in hexane to get the title compound (22.5 g).

Step c: Synthesis of (4S)-4-benzyl-1,3-thiazolidin-2-one

To a solution (4*S*)-4-benzyl-1,3-thiazolidine-2-thione (38 g) in dichloromethane (350 mL), cooled to 0°C was added propylene oxide (12.7 mL) and trifluoroacetic acid (14 mL). After stirring the reaction mixture for 2 hours, the solvents were evaporated under reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 20% ethylacetate in hexane as eluant to afford the title compound (0.9 g). Mass (m/z): 194.18

Step d: Synthesis of 3-{4-[(4S)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-4-oxobutyl}-1,2,3-benzotriazin-4(3H)-one

To a solution of compound (2.1g), obtained from step c above, in dichloromethane (25 mL) cooled to 0°C, 4-dimethylaminopridine (0.334 g) and triethylamine (5.7 mL) were added. After stirring the reaction mixture for 10 minutes, 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (3.9g) and 4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)butanoic acid (3 g) were added and the reaction mixture was stirred at room temperature for 14 hours. Dichloromethane and water were added to the reaction mixture. The organic layer was separated, washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 25% ethylacetate in hexane as eluant to afford the title compound (4.4 g). Mass (m/z): 409.16

The following analogue of 3-{4-[(4S)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-4-oxobutyl}-1,2,3-benzotriazin-4(3H)-one was prepared analogously:

3-{3-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-3-oxopropyl}-1,2,3-benzotriazin-4(3*H*)-one

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

Step a: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-D-arabinofuranose

D-Arabinose (200 g) and imidazole (199 g) were placed in a three-neck round bottom flask and connected to high vacuum for 30 minutes. The vacuum was released under nitrogen atmosphere and dimethylformamide (1.8 L) was added to the above mixture at room temperature followed by drop wise addition of *t*-butyldiphenylchlorosilane (443 mL) for 10 minutes under a nitrogen atmosphere. The resulting mixture was stirred for 16 hours at the same temperature. Dimethylformamide was evaporated under the reduced pressure. The residue was taken up in ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure to obtain a crude residue which was purified by column chromatography over silica gel using 80% ethyl acetate in hexane as eluant to afford the title compound (273 g). Mass (m/z): 389.37(M^+ +1)

Step b: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-1,2-O-isopropylidene-β-D-arabinofuranose

To the solution of compound (273 g), obtained from step a above, in acetone (2.5 L) was charged DL-camphorsulphonic acid (16 g) and anhydrous copper sulphate (346 g) under a nitrogen atmosphere at room temperature. The reaction mixture was stirred for 16 hours at the same temperature. A saturated solution of sodium bicarbonate (2 L) was added dropwise till a basic pH was attained, and the reaction mixture was further stirred for 2 hours at the same temperature. The resulting mixture was filtered using a Buchner funnel and the residue was washed with acetone. The filtrate was concentrated, dissolved in ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to furnish the title compound (295 g). Mass (m/z): 429.41(M^+ +1)

Step c: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-1,2-O-isopropylidene-β-D-threo-pentofuranos-3-ulose

Oxalyl chloride (145 ml) and dichloromethane (1 L) were taken in a three neck round bottom flask and cooled to -75 ℃ under a nitrogen atmosphere. Dimethylsulfoxide (212 mL) was added dropwise to the above solution maintaining the reaction temperature at -70 ℃. The reaction mixture was stirred for 30 minutes at the same temperature, then a solution of the compound (285 g) obtained from step b above, in dichloromethane (1 L), was added slowly to the above mixture, maintaining the reaction temperature -70 ℃. After 20 minutes of the above addition, triethylamine (560 mL) was added drop wise at the same temperature. Saturated solution of ammonium chloride in water (1.5 L) was then added after 30 minutes and the reaction temperature was allowed to rise to room temperature. The reaction mixture was extracted with dichloromethane. Organic extracts were dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to afford the title compound (285 g)

Step d: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-ethoxy-2-oxoethylidene)-1,2-O-isopropylidene-β-D-arabinofuranose

To the suspension of sodium hydride (29.4 g, 60% in oil.) in tetrahydrofuran (1L) at 0 ℃ was charged triethyl phosphonoacetate (200 mL). After 20 min, a solution of compound (285 g), obtained from step c above, in tetrahydrofuran (2 L) was added dropwise and the reaction mixture was stirred for 1 hour at the same temperature. A saturated solution of ammonium chloride in water (1.5 L) was added to reaction mixture. The resulting mixture was extracted with ethyl acetate. Combined extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure to yield a residue which was purified by column chromatography over silica gel using 15% ethyl acetate in hexane as eluant to afford the title compound (275 g). Mass (m/z): 497.43 (M^+ +1)

Step e: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-ethoxy-2-oxoethyl)-1,2-O-isopropylidene-β-D-lyxofuranose and 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-ethoxy-2-oxoethyl)-1,2-O-isopropylidene-α-L-ribofuranose

10% Palladium on charcoal (100 g) was added to the solution of compound (275 g), obtained from step d above, in tetrahydrofuran (2 L) and methanol (1 L) at room temperature and hydrogen was supplied at 50 psi (Paar apparatus) for 2 hours. The

reaction mixture was filtered through a celite pad and the residue was washed with ethyl acetate. The filterate was concentrated to afford a mixture of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-ethoxy-2-oxoethyl)-1,2-O-isopropylidene-β-D-lyxofuranose and 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-ethoxy-2-oxoethyl)-1,2-O-isopropylidene-α-L-ribofuranose (275 g). Mass (m/z): 499.42 (M^+ +1)

Step f: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-hydroxyethyl)-1,2-O-isopropylidene-β-D-lyxofuranose and 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-hydroxyethyl)-1,2-O-isopropylidene-α-L-ribofuranose

To the suspension of lithium aluminium hydride (48 g) in tetrahydrofuran (1 L) was added a solution of compound (275 g), obtained from step e above, in tetrahydrofuran (1.5 L) at -50°C. The resulting mixture was allowed to attain 0°C. The reaction mixture was stirred for 30 minutes at same temperature and again cooled to -50°C. Ethyl acetate (2 L) was added slowly while maintaining -50°C. An aqueous solution of ammonium chloride (100 g) in water (2.5 L) was added at the same temperature. The reaction mixture was slowly allowed to warm to room temperature and the reaction mixture was stirred for 12 hours at same temperature. The reaction mixture was then filtered through a celite pad and the residue was washed with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered, concentrated under reduced pressure and the residue thus obtained was purified by column chromatography over silica gel using 50% ethyl acetate in hexane as eluant to afford the 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-hydroxyethyl)-1,2-O-isopropylidene-β-D-lyxofuranose (130 g) and 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-hydroxyethyl)-1,2-O-isopropylidene-α-L-ribofuranose (40.0 g). Mass (m/z): 457.39(M^+ +1).

Step g: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-1,2-O-isopropylidene-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-β-D-lyxofuranose

5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-hydroxyethyl)-1,2-O-isopropylidene-β-D-lyxofuranose (35g), triphenylphosphine (30.8g) and 1,2,3-benzotriazin-4(3*H*)-one (12.6g) were dried in high vacuum in a round bottom flask for 10 minutes. Then the vacuum was released under a nitrogen atmosphere and tetrahydrofuran (70mL) was added to the above reaction mixture. The reaction mixture was cooled to 0°C and diisopropyl azodicarboxylate (17mL) was added slowly. The reaction mixture was stirred for 30

minutes at same temperature, and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated to obtain a residue which was purified by column chromatography over silica gel using 30% ethyl acetate in hexane as eluant to afford the title compound (50g). Mass (m/z):586.05 (M^+ +1)

Step h: Synthesis of 3-deoxy-1,2-O-isopropylidene-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-β-D-lyxofuranose

To a solution of compound (50g), obtained from step g above, in dry tetrahydrofuran (400mL) at 0°C, was added tetra-butyl ammonium fluoride (170mL). The resulting mixture was initially stirred at 0°C for 1hour, and then at room temperature for 4 hours. The reaction mixture was cooled to 0°C, quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulphate and concentrated. The residue thus obtained was purified by column chromatography over silica gel using 80% ethyl acetate in hexane as eluant to furnish the title compound (22 g).

Mass (m/z):369.98 (M^+ +23)

Step i: Synthesis of (5S)-3-deoxy-4,5-O-isopropylidene-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-D-arabino-pentodialdo-5,2-furanose

Oxalyl chloride (13.7mL) and dichloromethane (300mL) were taken in a three neck round bottom flask and cooled to -78 °C. Dimethylsulfoxide (20.2mL) was added dropwise to the reaction mixture. The reaction mixture was warmed to -35°C for 5 to 10 minutes and again cooled to -78°C. A solution of compound (22 g), obtained from step h above, in dichloromethane (200mL) was added slowly while maintaining the same temperature. The reaction mixture was stirred for 45 minutes till the reaction temperature reached -35°C. The reaction mixture was again cooled to -78°C and triethylamine (53mL) was added. The reaction mixture was stirred for an additional 30 minutes, and the temperature was allowed to reach -35°C. The reaction mixture was quenched with saturated solution of ammonium chloride and extracted with dichloromethane. The combined organic layers were washed with water and brine solution, dried over anhydrous sodium sulphate and concentrated to furnish the title compound (22g).

Step j: Synthesis of 3-(2-{(3aS,5R,6S,6aS)-5-[(E)-2-(4-bromophenyl)vinyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one

To the suspension of sodium hydride (3.3g, 60% in oil) in tetrahydrofuran (50mL) cooled to 0°C, was added (4-bromobenzyl)triphenylphosphonium bromide (48.8g) in tetrahydrofuran (100mL). A solution of compound (22g), obtained from step i above, in tetrahydrofuran (100mL) was added dropwise after 20 minutes, and reaction mixture was stirred for 1 hour at the same temperature. The reaction mixture was quenched with water and extracted with ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography using 30% ethyl acetate in hexane as eluant to furnish the title compound (24.5g). Mass (m/z):498.84 (M^+ +1)

Step k: Synthesis of 3-(2-{(3aS,5R,6S,6aS)-2,2-dimethyl-5-[(E)-2-(4-pyrimidin-5-ylphenyl)vinyl]tetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one

A mixture of compound (0.35g), obtained from step j above, pyrimidin-5-ylboronic acid (0.174g), tetrakistriphenylphosphinepalladium (0) (0.081g) and potassium carbonate (0.291g) was dried under high vacuum for 10 minutes and dry dimethylformamide (5mL) was added at room temperature. The reaction mixture was heated at 120°C for 2 hours, and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 40% ethyl acetate in hexane as eluant to afford the title compound (0.3g). Mass (m/z): 498.0(M^+ +1)

Step l: Synthesis of 3-(2-{(3aS,5R,6S,6aS)-2,2-dimethyl-5-[2-(4-pyrimidin-5-ylphenyl)ethyl]tetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one

To the solution of compound (0.3g), obtained from step k above, in a solvent mixture of tetrahydrofuran: methanol (10mL, 1:1) was added 10% Palladium on charcoal (0.15g) at room temperature and the reaction mixture was hydrogenated with hydrogen at the pressure of 35 psi for 4 hours in a Paar apparatus. The reaction mixture was filtered

through a celite pad and the residue was washed with methanol. The filtrate was concentrated to afford the title compound (0.3g).

Step m: Synthesis of 3-(2-{(2R,3R,4S,5R)-4,5-dihydroxy-2-[2-(4-pyrimidin-5-ylphenyl)ethyl]tetrahydrofuran-3-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one

Perchloric acid (0.2mL) was added to a solution of compound (0.3g), obtained from step l above, in acetonitrile (4mL) and water (0.2mL) at room temperature. The reaction mixture was heated to 55°C for 30 minutes. The reaction mixture was then quenched using sodium bicarbonate solution. The solvents were evaporated under reduced pressure. The residue thus obtained was taken up in ethyl acetate and water. The organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was concentrated under reduced pressure to yield the title compound (0.25g).

Step n: Synthesis of (2S,3R)-3-(formyloxy)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4-pyrimidin-5-ylphenyl)pentanoic acid

To a solution of compound (0.25g), obtained from step m above, in *tert*-butanol: tetrahydrofuran (5mL:5mL) at 0°C was added a solution of sodium metaperiodate (0.465 g in 5 mL of water). The reaction mixture was stirred for 2 hours at the same temperature and potassium permangnate (0.017g) was added at 0°C. After stirring the reaction mixture for an additional 6 hours at room temperature, the reaction mixture was evaporated on rotary evaporator. The residue was taken into water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure, to afford the title compound (0.25g).

Step o: Synthesis of (2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4-pyrimidin-5-ylphenyl)pentanoic acid

Potassium carbonate (0.081g) was added to a solution of compound (0.25g), obtained from step n above, in methanol (5mL) and tetrahydrofuran (5mL) at 0°C. The reaction mixture was stirred at room temperature for 3 hours. Solvents were evaporated and the residue was taken into water and ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure to obtain a residue which was purified by column

chromatography over silica gel using 60% ethyl acetate in hexane as eluant to afford the title compound (0.030g). Mass (m/z):446.0 (M^+ +1).

^{1}HNMR (CD_3OD): δ 9.09 (s, 1H), 9.03 (s, 1H), 8.30 (d, 1H, J = 8Hz), 8.14 (d, 1H, J = 8Hz), 8.05- 8.03 (m, 1H), 7.89-7.87 (m, 1H), 7.61 (d, 2H, J = 8Hz), 7.53- 7.59 (m,1H), 7.35 (d, 2H, J = 8Hz), 4.57- 4.52 (m, 2H), 3.79-3.77 (m, 1H), 2.89 -2.87 (m, 1H), 2.69 - 2.67 (m, 1H), 2.47- 2.46 (m, 1H), 2.29- 2.25 (m, 2H), 1.82- 1.77 (m, 2H).

Example 1A: Synthesis of (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. 86)

Step a: Synthesis of 3-(2-{(3a*S*,5*R*,6*S*,6a*S*)-5-[(*E*)-2-(4-bromophenyl)ethenyl]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl}ethyl)-1,2,3-benzotriazin-4(3*H*)-one

To the suspension of potassium t-butoxide (3.3g, 60% in oil) in dimethyl sulfoxide (50mL) cooled to 0℃, was added 4-bromobenzyl triphenyl-phosphonium bromide (48.8g) in dimethyl sulfoxide (100mL). After 20 minutes, compound (22g) obtained from step i of example 1 above, was added in dimethyl sulfoxide (100mL) drop wise and reaction mixture was stirred for 1 hour at the same temperature. Reaction mixture was quenched with water and extracted with ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure. Purification was performed on silica gel column by using 30% ethyl acetate in hexane as eluent to get the title compound (24.5g).

Step b: Synthesis of 3-{2-[(3a*S*,5*R*,6*S*,6a*S*)-5-{(*E*)-2-[4-(6-methoxypyridin-3-yl)phenyl]ethenyl}-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl]ethyl}-1,2,3-benzotriazin-4(3*H*)-one

A mixture of compound (12gms), obtained from step a above, 2-methoxy-5-pyridine boronic acid (7.4gms), tetrakistriphenylphosphinepalladium (0) (2.8gms) and potassium carbonate (10gms) was dried under high vacuum for 10 minutes and dry dimethylformamide (60ml) was added at room temperature. The reaction mixture was heated at 120°C for 2 hours, and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 40% ethyl acetate in hexane as eluant to afford the title compound (8.5gms).

Step c: Synthesis of 3-{2-[(3a*S*,5*R*,6*S*,6a*S*)-5-{2-[4-(6-methoxypyridin-3-yl)phenyl]ethyl}-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl]ethyl}-1,2,3-benzotriazin-4(3*H*)-one

To the solution of compound (8.5g), obtained from step b above, in a solvent mixture of tetrahydrofuran: methanol (60mL:40mL) was added 10% Palladium on charcoal (4g) at room temperature and the reaction mixture was hydrogenated with hydrogen at the pressure of 35 psi for 4 hours in a Paar apparatus. The reaction mixture was filtered through a celite pad and the residue was washed with methanol. The filtrate was concentrated to afford the title compound (8.1g).

Step d: Synthesis of 3-{2-[(2*R*,3*R*,4*S*,5*R*)-4,5-dihydroxy-2-{2-[4-(6-methoxypyridin-3-yl)phenyl]ethyl}tetrahydrofuran-3-yl]ethyl}-1,2,3-benzotriazin-4(3*H*)-one

Perchloric acid (4.8ml) was added to a solution of compound (8.1gms), obtained from step c above, in acetonitrile (50ml) and water (8ml) at room temperature. The reaction mixture was heated to 55°C for 30 minutes. The reaction mixture was then quenched using sodium bicarbonate solution. The solvents were evaporated under reduced pressure. The residue thus obtained was taken up in ethyl acetate and water. The organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was concentrated under reduced pressure to yield the title compound (8gm).

Step e: Synthesis of (2*S*,3*R*)-3-(formyloxy)-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid

To a solution of compound (8g), obtained from step d above, in *tert*-butanol: tetrahydrofuran (40mL:40mL) at 0°C was added a solution of sodium metaperiodate (14g in 40 mL of water). The reaction mixture was stirred for 2 hours at the same temperature and potassium permangnate (518mg) was added at 0°C. After stirring the reaction mixture for an additional 6 hours at room temperature, the reaction mixture was evaporated on rotary evaporator. The residue was taken into water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure, to afford the title compound (8g).

Step f: Synthesis of (2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid

Potassium carbonate (2.3g) was added to a solution of compound (8g), obtained from step e bove, in methanol (40mL) and tetrahydrofuran (30mL) at 0°C. The reaction mixture was stirred at room temperature for 3 hours. Solvents were evaporated and the residue was taken into water and ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 60% ethyl acetate in hexane as eluant to afford the title compound (3g). **Mass (m/z):** 474.87(M^+ +1); **^{1}H NMR (400 MHz, MeOD):** δ 8.32- 8.30 (2H, m), 8.16- 8.14 (1H, m), 8.04- 8.03 (1H, m), 7.92- 7.88 (2H, m), 7.46 (2H, d, J= 8Hz), 7.24 (2H, m, J= 8Hz), 6.86 (1H, d, J= 8Hz), 4.57- 4.53 (2H, m), 3.93 (3H, s), 3.78-3.83 (1H, m), 2.83- 2.80 (1H, m), 2.63- 2.60 (1H, m), 2.52- 2.49 (1H, m), 2.32- 2.28 (2H, m), 1.80-1.76 (2H, m).

Example 1B: Synthesis of (2*S*,3*R*)-3-hydroxy-5-[4-(6-hydroxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 226)

To a solution of compound(0.2 gm), obtained from Example1A above in dry toluene (5ml), cooled to –78 ℃, was added boron tribromide (0.5 ml) and the contents were stirred at room temperature for 4 hours. Ethyl acetate and water were added to the reaction mixture. Organic layer was separated, washed with water and brine and dried over anhydrous sodium sulfate. Solvent was evaporated to obtain a residue which was purified by preparatory thin layer chromatography (2 mm thickness) using 15% methanol in dichloromethane as eluent to get the title compound (60mg). **Mass (m/z):** 461.23 (M^+ +1); **^{1}HNMR (CD_3OD):** 8.30 (d, 1H, J = 8Hz), 8.15 (d, 1H, J = 8Hz), 8.06-8.01 (m, 2H), 7.88 (t, 1H, J = 8Hz), 7.79-7.76 (m, 1H), 7.43 (d, 2H, J = 12Hz), 7.25 (d, 2H, J = 12Hz), 6.75 (d, 1H, J = 12Hz), 4.58- 4.51 (m, 2H), 3.82-3.76 (m, 1H), 2.88 -2.78 (m, 1H), 2.66 - 2.57 (m, 1H), 2.54- 2.47 (m, 1H), 2.33- 2.25 (m, 2H), 1.84- 1.70 (m, 2H).

Example 1C: Synthesis of (2*S*,3*R*)-3-(acetyloxy)-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 229)

Diisopropyl azodicarboxylate (63 mg) was added to a solution of compound (100 mg) obtained from Example1A above, tri-n-butylphosphine (93 mg) and acetic acid (1 ml)

in dry tetrahydrofuran (3 ml) at 0°C. Reaction mixture was stirred for 1hour and concentrated. Residue was taken in ethyl acetate and washed with water and brine. Organic layer was concentrated to get oily residue which was purified on preparative thin layer chromatography (2 mm thickness) using 10% methanol in dichloromethane to get the title compound (80 mg) (formed probably by esterfication of acetic acid (used in large excess) and not due to Mitsunobu reaction). **Mass (m/z):** 517.06 (M^+ +1); **^{1}HNMR:** δ 8.37 (m, 2H), 8.15 (d, 1H, J = 8Hz), 7.97- 7.93 (m, 1H), 7.82- 7.80 (m, 1H), 7.41(d, 2H, J = 8Hz), 7.20 (d, 2H, J = 8Hz), 6.83 (d, 1H, J = 8Hz), 5.28- 5.27 (m, 1H), 4.56- 4.58 (m, 2H), 4.01 (s, 3H), 2.85- 2.80 (m, 1H), 2.55- 2.75 (m, 2H), 2.31- 2.29 (m, 2H), 2.25- 2.10 (m, 2H), 2.063 (s, 3H).

Example 1D: Synthesis of (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.88)

Step a: Synthesis of 5-*O*-[*tert*-butyl(diphenyl)silyl]-3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1,2-*O*-(1-methylethylidene) -β -D-lyxofuranose

5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-(2-hydroxyethyl)-1,2-O-isopropylidene-β-D-lyxofuranose (14g), triphenylphosphine (12g) and phthalimide (5g) were dried in high vacuum in a round bottom flask for 10 minutes. Then the vacuum was released under a nitrogen atmosphere and tetrahydrofuran (100mL) was added to the above reaction mixture. The reaction mixture was cooled to 0°C and diethyl azodicarboxylate (7.8mL) was added slowly. The reaction mixture was stirred for 30 minutes at same temperature, and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated to obtain a residue which was purified by column chromatography over silica gel using 30% ethyl acetate in hexane as eluant to afford the title compound (11g).

Step b: Synthesis of 3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1,2-*O*-(1-methylethylidene)- β-D-lyxofuranose

To a solution of compound (11g), obtained from step a above, in dry tetrahydrofuran (50mL) at 0°C, was added tetra-butyl ammonium fluoride (41.36mL). The resulting mixture was initially stirred at 0°C for 1hour, and then at room temperature for 4 hours. The reaction mixture was cooled to 0°C, quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water and

brine, dried over anhydrous sodium sulphate and concentrated. The residue thus obtained was purified by column chromatography over silica gel using 80% ethyl acetate in hexane as eluant to furnish the title compound (5 g).

Step c: Synthesis of (5*S*)-3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-4,5-*O*-(1-methylethylidene)-D-*arabino*-pentodialdo-5,2-furanose

Oxalyl chloride (4.5mL) and dichloromethane (20mL) were taken in a three neck round bottom flask and cooled to -78^{0}C. Dimethylsulfoxide (6.6mL) was added dropwise to the reaction mixture. The reaction mixture was warmed to -35°C for 5 to 10 minutes and again cooled to -78°C. A solution of compound (7.2 g), obtained from step b above, in dichloromethane (20mL) was added slowly while maintaining the same temperature. The reaction mixture was stirred for 45 minutes till the reaction temperature reached -35°C. The reaction mixture was again cooled to -78°C and triethylamine (17.3mL) was added. The reaction mixture was stirred for an additional 30 minutes, and the temperature was allowed to reach -35°C. The reaction mixture was quenched with saturated solution of ammonium chloride and extracted with dichloromethane. The combined organic layers were washed with water and brine solution, dried over anhydrous sodium sulphate and concentrated to furnish the title compound (7.3g).

Step d: Synthesis of 2-(2-{(3a*S*,5*R*,6*S*,6a*S*)-5-[(*E*)-2-(4-bromophenyl)ethenyl]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl}ethyl)-1*H*-isoindole-1,3(2*H*)-dione

To the suspension of potassium t-butoxide (2.3g) in dimethyl sulfoxide (30ml) cooled to 0^0 C, was added (4-bromobenzyl)triphenylphosphonium bromide (12.2gm) in dimethyl sulfoxide (20ml). After 20 minutes, a solution of compound (4.1gms) obtained from step c above, in dimethyl sulfoxide (10ml) was added drop wise and reaction mixture was stirred for 1 hour at the same temperature.Reaction mixture was quenched with water and extracted with ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure. Purification was performed on silica gel column by using 40% ethyl acetate in hexane as eluant to furnish the title compound (4gms).

Step e: Synthesis of 2-{2-[(3a*S*,5*R*,6*S*,6a*S*)-5-{(*E*)-2-[4-(6-methoxypyridin-3-yl)phenyl]ethenyl}-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione

A mixture of compound (1g), obtained from step d above, 2-methoxy-5-pyridine boronic acid (0.614g), tetrakistriphenylphosphinepalladium (0) (0.115g) and potassium carbonate (0.832g) was dried under high vacuum for 10 minutes and dry dimethylformamide (8mL) was added at room temperature. The reaction mixture was heated at 120°C for 2 hours, and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 30% ethyl acetate in hexane as eluant to afford the title compound (0.62g).

Step f: Synthesis of 2-{2-[(3a*S*,5*R*,6*S*,6a*S*)-5-{2-[4-(6-methoxypyridin-3-yl)phenyl]ethyl}-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione

To the solution of compound (0.6g), obtained from step e above, in a methanol (10mL, was added 10% Palladium on charcoal (0.05g) at room temperature and the reaction mixture was hydrogenated with hydrogen at the pressure of 35 psi for 4 hours in a Paar apparatus. The reaction mixture was filtered through a celite pad and the residue was washed with methanol. The filtrate was concentrated to afford the title compound (0.56g).

Step g: Synthesis of 2-{2-[(2*R*,3*R*,4*S*,5*R*)-4,5-dihydroxy-2-{2-[4-(6-methoxypyridin-3-yl)phenyl]ethyl}tetrahydrofuran-3-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione

Perchloric acid (0.4mL) was added to a solution of compound (0.5g), obtained from step f above, in acetonitrile (4mL) and water (0.8mL) at room temperature. The reaction mixture was heated to 55°C for 30 minutes. The reaction mixture was then quenched using sodium bicarbonate solution. The solvents were evaporated under reduced pressure. The residue thus obtained was taken up in ethyl acetate and water. The organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was concentrated under reduced pressure to yield the title compound (0.51g).

Step h: Synthesis of (1*R*,2*S*)-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-formyl-1-{2-[4-(6-methoxypyridin-3-yl)phenyl]ethyl}butyl formate

To a solution of compound (0.56g), obtained from step g above, in methanol (4mL) at 0°C was added a solution of sodium metaperiodate (0.736 g in 1 mL of water). The reaction mixture was stirred for 2 hours at the same temperature. After stirring the reaction mixture for an additional 1hour at room temperature, the reaction mixture was evaporated on rotary evaporator. The residue was taken into water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure to obtained the title compound (0.54g).

Step i: Synthesis of (2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-(formyloxy)-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid

The compound (0.54 g) obtained was taken in acetonitrile (6mL) and water (1mL).To this solution, sodiumdihydrogen phosphate (0.054g) was added. Reaction mixture was cooled to 0°C and hydrogen peroxide (1mL) and sodium chlorite (0.208 g) were added. After stirring the reaction mixture for additional 1hour, solvents were evaporated on rotaevaporator; the residue was taken into water and extracted with ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure, to get the title compound (0.5 g)

Step j: Synthesis of (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

Potassium carbonate (0.165g) was added to a solution of compound (0.4g), obtained from step i above, in methanol (6mL) at 0°C. The reaction mixture was stirred at room temperature for 3 hours. Solvents were evaporated and the residue was taken into water and ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure to obtain a residue which was purification with preparatory TLC using 7% methanol in ethylacetate as eluent to get the title compound (0.13gm). **Mass (m/z):** 474.88(M^+ +1); **^{1}HNMR ($CDCl_3$):-** δ 8.35 (s, 1H), 7.83-7.81 (m, 2H), 7.77-7.69 (m, 3H), 7.42 (d, 2H, J =

3Hz), 7.25 (d, 2H, J = 6Hz), 6.80 (d, 1H, J = 6Hz), 3.97 (s, 3H), 3.87-3.78 (m, 3H), 2.89(m, 1H), 2.69 (m, 1H), 2.57(m, 1H), 2.15-1.98 (m, 2H), 1.84-1.79 (m, 2H);

Example 1E: Synthesis of (2S,3R)-5-(2',4'-difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 97)

Step a: Synthesis of 2-(2-{(3a*S*,5*R*,6*S*,6a*S*)-5-[(*E*)-2-(3',5'-difluorobiphenyl-4-yl)ethenyl]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl}ethyl)-1*H*-isoindole-1,3(2*H*)-dione

A mixture of compound (0.2g), obtained from step d of Example 1D above, 3,5-difluorophenyl boronic acid (0.135g), tetrakistriphenylphosphinepalladium (0) (0.023g) and potassium carbonate (0. 2g) was dried under high vacuum for 10 minutes and dry dimethylformamide (3mL) was added at room temperature. The reaction mixture was heated at 120°C for 2 hours, and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 30% ethyl acetate in hexane as eluant to afford the title compound (0.205g).

Step b: Synthesis of 2-(2-{(3a*S*,5*R*,6*S*,6a*S*)-5-[2-(3',5'-difluorobiphenyl-4-yl)ethyl]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl}ethyl)-1*H*-isoindole-1,3(2*H*)-dione

To the solution of compound (0.2g), obtained from step a above, in a tetrahydrofuran (10mL), was added 10% Palladium on charcoal (0.1g) at room temperature and the reaction mixture was hydrogenated with hydrogen at the pressure of 35 psi for 4 hours in a Paar apparatus. The reaction mixture was filtered through a celite pad and the residue was washed with methanol. The filtrate was concentrated to afford the title compound (0.2g).

Step c: Synthesis of 2-(2-{(2*R*,3*R*,4*S*,5*R*)-2-[2-(3',5'-difluorobiphenyl-4-yl)ethyl]-4,5-dihydroxytetrahydrofuran-3-yl}ethyl)-1*H*-isoindole-1,3(2*H*)-dione

Perchloric acid (0.3mL) was added to a solution of compound (0.2g), obtained from step b above, in acetonitrile (6mL) and water (2mL) at room temperature. The reaction mixture was heated to 55°C for 30 minutes. The reaction mixture was then quenched using sodium bicarbonate solution. The solvents were evaporated under

reduced pressure. The residue thus obtained was taken up in ethyl acetate and water. The organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was concentrated under reduced pressure to yield the title compound (0.15g).

Step d: Synthesis of (1*R*,2*S*)-1-[2-(3',5'-difluorobiphenyl-4-yl)ethyl]-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-formylbutyl formate

To a solution of compound (0.15g), obtained from step c above, in methanol (6mL) at 0°C was added a solution of sodium metaperiodate (0.15 g in 1 mL of water). The reaction mixture was stirred for 2 hours at the same temperature. After stirring the reaction mixture for an additional 1hour at room temperature, the reaction mixture was evaporated on rotary evaporator. The residue was taken into water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure to obtained the title compound (012g).

Step e: Synthesis of (2*S*,3*R*)-5-(3',5'-difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-(formyloxy)pentanoic acid

The compound (0.12 g) obtained from step d was taken in acetonitrile (6mL) and water (1mL), to this solution sodiumdihydrogen phosphate (0.05g) was added. Reaction mixture was cooled to 0°C and hydrogen peroxide (0.5mL) and sodium chlorite (0.15 g) were added. After stirring the reaction mixture for additional 1hour, solvents were evaporated on rotaevaporator, the residue was taken into water and extracted with ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure, to get the title compound (0.12 g)

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

Potassium carbonate (0.06g) was added to a solution of compound (0.12g), obtained from step e above, in methanol (10mL) at 0°C. The reaction mixture was stirred at room temperature for 3 hours. Solvents were evaporated and the residue was taken into water and ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure to

obtain a residue which was purification with preparatory thin layer chromatography using 10% methanol in ethylacetate as eluent to get the title compound (0.025gm). **Mass (m/z):** 480.13(M^+ +1);^{1}**HNMR (CD_3OD):** δ 7.48-7.76 (m, 4H), 7.47-7.37 (m, 3H), 7.25-7.23 (d, 2H), 7.03-6.98 (m, 2H), 3.78-3.72 (m, 3H), 2.85-2.81 (m 1H), 2.65-2.63 (m, 1H), 2.422.40 (m, 1H), 2.10-2.05 (m, 2H), 1.79-1.75 (m, 2H);

Example 2: Synthesis of (2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid (Compound No. 82)

Step a: Synthesis of 3-{2-[(3aS,5R,6S,6aS)-2,2-dimethyl-5-(2-phenylethyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-yl]ethyl}-1,2,3-benzotriazin-4(3H)-one

To the solution of compound (0.3g), obtained from step j of Example 1, in a solvent mixture of tetrahydrofuran: methanol (10mL:10 mL) was added palladium/carbon (0.2 g, 10%) at room temperature and the reaction mixture was hydrogenated at the pressure of 35 psi for 4 hours in a Paar apparatus. The reaction mixture was filtered through a celite pad and the residue was washed with methanol. The filtrate was concentrated to afford the title compound (0.3 g). Mass (m/z):421 (M^+)

Step b: Synthesis of 3-{2-[(2R,3R,4S,5R)-4,5-dihydroxy-2-(2-phenylethyl)tetrahydrofuran-3-yl]ethyl}-1,2,3-benzotriazin-4(3H)-one

Perchloric acid (0.2 mL) was added to a solution of compound (0.3g), obtained from step a above, in acetonitrile (4 mL) and water (0.3 mL) at room temperature. The reaction mixture was heated to 55°C for 30 minutes. The reaction mixture was then quenched using a sodium bicarbonate solution. The solvents were evaporated at reduced pressure. The residue thus obtained was taken up in ethyl acetate and water. The organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was concentrated under reduced pressure to yield the title compound (0.3 g).

Step c: Synthesis of (2S,3R)-3-(formyloxy)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid

To a solution of compound (0.3 g), obtained from step b above, in a *tert*-butanol:tetrahydrofuran (3mL:3mL) at 0°C was added a solution of sodium metaperiodate

(0.673 g in 3mL of water). The reaction mixture was stirred for 2 hours at same temperature and potassium permangnate (0.025 g) was added at 0°C. After stirring the reaction mixture for an additional 6 hours at room temperature, the reaction mixture was evaporated, the residue was taken into water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure, to afford the title compound (0.3 g).

Step d: Synthesis of (2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid

Potassium carbonate (0.11 g) was added to a solution of compound (0.3 g), obtained from step c above, in methanol (4mL) and tetrahydrofuran (4mL) at 0°C. The reaction mixture was stirred at room temperature for 3 hours. The solvents were evaporated and the residue was taken into water and ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 10% methanol in dichloromethane as eluant to afford the title compound (0.020g). Mass (m/z):368.0 (M^+ +1); ^{1}HNMR (CD_3OD): δ 8.31 (d, 1H, J = 8Hz), 8.15 (d, 1H, J = 8Hz), 8.06- 8.02 (m, 1H), 7.91- 7.89 (m, 2H), 7.62 (d, 2H, J = 8Hz), 7.36 (d, 1H, J = 8Hz), 7.21-7.07 (m, 1H), 4.57- 4.52 (m, 2H), 3.78-3.76 (m, 1H), 2.76 -2.75 (m, 1H), 2.57 - 2.49 (m, 2H), 2.29- 2.27 (m, 2H), 1.74- 1.71 (m, 2H).

Example 3: Synthesis of (2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4(trifluoromethyl)phenyl]pentanoic acid (Compound No.84)

Step a: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-1,2-O-isopropylidene-β-D-lyxofuranose

A mixture of compound (0.14g), obtained from step f of Example 1, triphenylphosphine (0.080g) and pthalimide (0.045g) were taken in a round bottom flask and dried in high vacuum for 10 minutes. The vacuum was released under a nitrogen atmosphere and tetrahydrofuran (5mL) was added to the reaction mixture. The reaction mixture was cooled to 0°C and diethyl azodicarboxylate (0.1 mL) was added slowly. The reaction mixture was stirred for 30 minutes at same temperature and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine

solution, dried over anhydrous sodium sulphate and concentrated. The residue thus obtained was purified by column chromatography over silica gel using 30 % ethyl acetate in hexane as eluant to afford the title compound (0.11g). Mass (m/z): 608 (M^+ +23)

Step b: Synthesis of 3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-1,2-O-isopropylidene-β-D-lyxofuranose

To a solution of compound (0.060g), obtained from step a above, in dry tetrahydrofuran (2 mL) at 0°C, was added tetra-butyl ammonium fluoride (0.2 mL). The resulting mixture was initially stirred at 0°C for 1 hour, and then at room temperature for 4 hours. The reaction mixture was cooled to 0°C, quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulphate and concentrated. The residue thus obtained was purified by column chromatography over silica gel using 60% ethyl acetate in hexane as eluant to furnish the title compound (0.4 g).

Step c: Synthesis of (5S)-3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4,5-O-isopropylidene-D-arabino-pentodialdo-5,2-furanose

In a three-neck round bottom flask, oxalyl chloride (0.6 mL) and dichloromethane (20 mL) were placed and cooled to -78^{0}C. Dimethylsulfoxide (1mL) was added dropwise to the reaction mixture. The reaction mixture was warmed to -35°C for 5 to 10 minutes and again cooled to -78°C. A solution of compound (1 g), obtained from step b above, in dichloromethane (5mL) was added slowly while maintaining the same temperature. The reaction mixture was stirred for 45 minutes till reaction temperature reached -35°C. The reaction mixture was again cooled to -78°C and triethylamine (2.4 mL) was added. The reaction mixture was stirred for an additional 30 minutes and the temperature was allowed to reach -35°C. The reaction mixture was quenched with saturated solution of ammonium chloride and extracted with dichloromethane. The combined organic layer was washed with water and brine solution, dried over anhydrous sodium sulphate and concentrated to furnish the title compound (1.0 g).

Step d: Synthesis of 2-{2-[(3aS,5R,6S,6aS)-2,2-dimethyl-5-{(E)-2-[4-(trifluoromethyl) phenyl]vinyl}tetrahydrofuro[2,3-d][1,3]dioxol-6-yl]ethyl}-1H-isoindole-1,3(2H)-dione

To the suspension of triphenyl[4-(trifluoromethyl)benzyl]phosphonium bromide (0.795 g) in dimethylsulphoxide (5 mL), potassium tert-butoxide (0.292g) was added. A solution of compound (0.5 g), obtained from step c above, in tetrahydrofuran (7 mL) was added dropwise after 20 minutes, and the reaction mixture was stirred for 1 hour at the same temperature. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography using 30% ethyl acetate in hexane as eluant to furnish the title compound (0.25g). Mass (m/z):487 (M^+)

Step e: Synthesis of 2-{2-[(3aS,5R,6S,6aS)-2,2-dimethyl-5-{2-[4-(trifluoromethyl)phenyl]ethyl}tetrahydrofuro[2,3-d][1,3]dioxol-6-yl]ethyl}-1H-isoindole-1,3(2H)-dione

10% Palladium on charcoal (0.2 g) was added to the solution of compound (0.25g), obtained from step d above, in ethyl acetate (20 mL) at room temperature and the reaction mixture was hydrogenated at 50 psi for 4 hours in a Paar apparatus. The reaction mixture was filtered through celite pad and the residue was washed with methanol. The filtrate was concentrated to afford the title compound (0.225 g).

Step f: Synthesis of 2-{2-[(2R,3R,4S,5R)-4,5-dihydroxy-2-{2-[4-(trifluoromethyl)phenyl]ethyl}tetrahydrofuran-3-yl]ethyl}-1H-isoindole-1,3(2H)-dione

Perchloric acid (0.2 mL) was added to a solution of compound (0.225 g), obtained from step e above, in acetonitrile (4mL), water (1 mL) and tetrahydrofuran (0.5 mL) at room temperature. The reaction mixture was heated to 55°C for 30 minutes. The reaction mixture was then quenched using sodium bicarbonate solution. The solvents were evaporated at reduced pressure. The residue thus obtained was taken in ethyl acetate and water. The organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was concentrated under reduced pressure to yield the title compound (0.22g).

Step g: Synthesis of (1R,2S)-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-formyl-1-{2-[4-(trifluoromethyl)phenyl]ethyl}butyl formate

A solution of sodium metaperiodate (0.313 g in 1 mL of water) was added to a solution of compound (0.22g), obtained from step f above, in a methanol:tetrahydrofuran(3 mL:1 mL) at 0°C. The reaction mixture was stirred for 2 hours at same temperature. After stirring the reaction mixture for an additional 6 hours at room temperature, the reaction mixture was evaporated on a rotary-evaporator, and the residue was taken into water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure, to afford the title compound (0.22 g).

Step h: Synthesis of (2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-(formyloxy)-5-[4-(trifluoromethyl)phenyl]pentanoic acid

To a solution of compound (0.22g), obtained from step g above, in a solvent mixture of acetonitrile:water (3mL:1mL) at 0°C, were added sodium dihydrogenphosphate (0.021g), sodium chlorite (0.081g) and hydrogen peroxide (1mL, 30% in water). The reaction mixture was stirred for 2 hours at room temperature. The solvents were evaporated under reduced pressure to obtain a residue. Ethyl acetate and water were added to the resulting residue. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure, to afford the title compound (0.2 g).

Step i: Synthesis of (2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(trifluoromethyl)phenyl]pentanoic acid

Potassium carbonate (0.178 g) was added to a solution of compound (0.2g), obtained from step h above, in methanol (7 mL) at 0°C. The reaction mixture was stirred at room temperature for 3 hours. The solvents were evaporated and the residue was taken into water and ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure obtain a residue which was purified by column chromatography over silica gel using 10 % methanol in dichloromethane as eluant to afford the title compound (0.090 g).

Mass (m/z): 458.0(M^+ +23)

^{1}HNMR (CD_3OD): δ 7.83 (q, 2H, J = 3.1 Hz), 7.71 (t, 2H, J = 3.2 Hz), 7.51 (d, 2H, J = 7.6 Hz), 7.28 (d, 2H, J = 7.9 Hz), 3.95-3.76 (m, 3H), 2.93-2.55 (m, 3H), 2.14-1.75 (m, 4H)

Example 4: Synthesis of (2R,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 89)

Step a: Synthesis of 1,2:5,6-Di-O-isopropyliden-α-D-ribo-3-hexulo-furanose

Oxalyl chloride (25.16 mL) and dichloromethane (200 mL) were taken in a three-neck round bottom flask and cooled to -75 ℃ under a nitrogen atmosphere. Then dimethylsulfoxide (27.3 mL) was added dropwise slowly maintaining the temperature at -70^{0}C. The reaction mixture was stirred for 30 minutes at the same temperature, and then diacetone-α-D-glucose (50 g) in dichloromethane (500 mL) was charged slowly maintaining the temperature at -70^{0}C. After 20 minutes, triethylamine (80 mL) was added dropwise to the above mixture at the same temperature. Saturated solution of ammonium chloride in water (500 mL) was charged to the reaction mixture after 30 minutes and the temperature was allowed to rise to room temperature. The reaction mixture was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford the title compound (45 g).

Step b : Synthesis of 1,2:5,6-Di-O-isopropylidene-3-deoxy-3-(2-ethoxy-2-oxoethylidene)- α -D-ribo-hexofuranose

To the suspension of sodium hydride (0.155 g, 60% in oil.) in tetrahydrofuran (5 mL) at 0^0 C was charged triethyl phosphonoacetate (1.55 mL). After 20 minutes, a solution of compound (1g), obtained from step a above, in tetrahydrofuran (3 mL) was added dropwise and the reaction mixture was stirred for 1 hour at the same temperature. A saturated solution of ammonium chloride was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate. Combined extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure to yield a residue which was purified by column chromatography over silica gel using 30 % ethyl acetate in hexane as eluant to afford the title compound (1.3 g). Mass (m/z): 351.1(M^+ +23)

Step c: Synthesis of 1,2:5,6-Di-O-isopropylidene-3-deoxy-3-(2-ethoxy-2-oxoethyl)- α -D-allofuranose

10% Palladium on charcoal (0.05 g) was added to the solution of compound (0.15 g), obtained from step b above, in ethyl acetate (10 mL) at room temperature and hydrogen

was supplied at 50 psi for 4 hours. The reaction mixture was filtered through a celite pad and the residue was washed with ethyl acetate. The filtrate was concentrated to afford the title compound (0.12g). Mass (m/z): 353.2 (M^+ +1).

Step d: Synthesis of 3-deoxy-3-(2-ethoxy-2-oxoethyl)-1,2-O-isopropylidene-α-D-allofuranose

30 % Perchloric acid (4 mL) was added to a solution of compound (2.0 g), obtained from step c above, in tetrahydrofuran (20 mL) at -5°C -0°C. The reaction mixture was stirred for 5 hours at -5°C -0°C and then quenched with saturated solution of sodium bicarbonate (20 mL). Solvents were evaporated, ethyl acetate and water were added to the resulting residue. The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate and concentrated to afford 1.5 g of the title compound. Mass (m/z):313.2 (M^+ +1)

Step e: Synthesis of 3-deoxy-3-(2-ethoxy-2-oxoethyl)-1,2-O-isopropylidene-α-D-ribo-pentodialdo-1,4-furanose

To a solution of compound (1.5 g), obtained from step d above, in methanol (15 mL) was added aqueous solution of sodium periodate (1.65 g in 10 mL of water) at 0°C. The reaction mixture was stirred for 3 hours from 0°C to room temperature. Solvents were evaporated. Ethyl acetate and water were added to the residue. The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate and concentrated to afford the title compound (0.9g). Mass (m/z):259.2 (M^+ +1)

Step f: Synthesis of ethyl {(3aR,5R,6R,6aR)-5-[(E)-2-(4-bromophenyl)vinyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}acetate

To the suspension of (4-bromobenzyl)triphenylphosphonium bromide (2.67g) in dimethylsulphoxide (15 mL), potassium *tert*-butoxide (0.508g) was added at 0℃. After stirring the reaction mixture for 30 minutes at room temperature, a solution of compound (0.9 g), obtained from step e above, in tetrahydrofuran (5 mL) was added dropwise at 0℃. The reaction mixture was stirred for 2 hours from 0℃ to room temperature, and quenched with ice cold water. Solvents were evaporated, and ethyl acetate and water were added to resulting residue. The organic layer was separated, washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography using 10

% ethyl acetate in hexane as eluant to furnish the title compound (1.0 g). Mass (m/z):413.3 (M^+ +1)

Step g: Synthesis of ethyl {(3aR,5R,6R,6aR)-5-[(E)-2-(4'-chlorobiphenyl-4-yl)vinyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}acetate

A mixture of compound (1.0g), obtained from step f above, (4-chlorophenyl)boronic acid (0.76 g), tetrakis(triphenylphosphine)palladium (0) (0.14 g) and potassium carbonate (1.0 g) in dry dimethylformamide (10 mL) was heated at 110°C for 4 hours. Ethyl acetate and water were added to the reaction mixture. The organic layer was separated, washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 12 % ethyl acetate in hexane as eluant to afford the title compound (0.9 g). Mass (m/z): 465.2 (M^+ +23)

Step h: Synthesis of ethyl {(3aR,5R,6R,6aR)-5-[2-(4'-chlorobiphenyl-4-yl)ethyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}acetate

To the solution of compound (0.8 g), obtained from step g above, in ethyl acetate (15 mL) was added 10% Palladium on charcoal (0.25 g) at room temperature. The system was evacuated with hydrogen and the reaction mixture was stirred for 4 hours at room temperature under a hydrogen atmosphere. The reaction mixture was filtered through celite pad and concentrated to afford the title compound (0.75 g). Mass (m/z): 415.4 (M^+ - 28)

Step i: Synthesis of 2-{(3aR,5R,6R,6aR)-5-[2-(4'-chlorobiphenyl-4-yl)ethyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethanol

To a solution of compound (0.75g), obtained from step h above, in tetrahydrofuran (15 mL) was added, lithium aluminium hydride (0.096 g) at 0°C. The resulting mixture was stirred for 3 hours at same temperature, and a saturated solution of ammonium chloride was then added. The reaction mixture was then filtered through silica gel (100-200 mesh) and concentrated. Ethyl acetate and water was added to the resulting residue. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate, filtered, concentrated under reduced pressure to afford the title compound (0.65 g). Mass (m/z): 425.2 (M^+ +23)

Step j: Synthesis of 2-{(3aR,5R,6R,6aR)-5-[2-(4'-chlorobiphenyl-4-yl)ethyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl methanesulfonate

Triethylamine (0.43 ml) and methanesulfonyl chloride (0.21 mL) were added to a solution of the compound (0.6 g) obtained from step i above, in dichloromethane (15 mL) at 0°C. The reaction mixture was stirred at room temperature for 2 hours. Dichloromethane and water were added to reaction mixture. The organic layer was separated, washed with water, dried and concentrated under reduced pressure to furnish the title compound (0.6g).

Step k: Synthesis of 2-(2-{(3aR,5R,6R,6aR)-5-[2-(4'-chlorobiphenyl-4-yl)ethyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1H-isoindole-1,3(2H)-dione

Potassium phthalimide (0.051 g) was added in one portion to a stirred solution of the compound (0.12 g), obtained from step j above, in dimethylformamide (5 mL) at room temperature under a nitrogen atmosphere. The resulting solution was heated at 50 °C for about 14 hours and then cooled to room temperature. Ethyl acetate and water were added to the reaction mixture. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate. The organic phase was evaporated to dryness under reduced pressure. The residue thus obtained was purified by column chromatography using 30 % ethyl acetate in hexane as eluant to furnish the title compound (0.1 g). Mass (m/z): 549.5 ($M^+ + NH_4^+$)

Step l: Synthesis of 2-(2-{(2R,3S,4R,5S)-2-[2-(4'-chlorobiphenyl-4-yl)ethyl]-4,5-dihydroxytetrahydrofuran-3-yl}ethyl)-1H-isoindole-1,3(2H)-dione

Trifluoroacetic acid (1mL) and water (0.5 mL) were added to compound (0.04g), obtained from step k above. The reaction mixture was stirred at room temperature for 2 hours. The solvents were evaporated at reduced pressure. The residue thus obtained was taken in ethyl acetate and water. The organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was concentrated under the reduced pressure to yield the title compound (0.028 g).

Step m: Synthesis of (2R,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-(formyloxy)pentanoic acid

To a solution of compound (0.028g), obtained from step l above, in a *tert*-butanol:water (2:3; 1.3 mL) was added sodium metaperiodate (0.051 g) at room

temperature. The reaction mixture was stirred for 2 hours at same temperature and potassium permangnate (0 .001 g) was added at 0°C. After stirring, the reaction mixture for additional 6 hours at room temperature, reaction mixture was evaporated on rotary evaporator, the residue was taken into water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure, to afford the title compound (0.025 g).

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

Potassium carbonate (0.007g) was added to a solution of compound (0.025 g), obtained from step m) above, in methanol (1 mL) at 0°C. The reaction mixture was stirred at room temperature for 3 hours. The solvents were evaporated and the residue was taken into water and ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure obtain a residue which was purified by column chromatography over silica gel using 10 % methanol in dichloromethane as eluant to afford the title compound (0.014 g). Mass (m/z):478.2 (M^+ +1)

^{1}HNMR (CD_3OD): δ 7.83 (q, 2H, J = 4Hz), 7.77 (q, 2H, J = 4Hz), 7.56 (d, 2H, J = 8Hz), 7.48 (d, 2H, J = 8Hz), 7.40 (d, 2H, J = 8Hz), 7.26 (d, 1H, J = 8Hz), 3.83-3.70 (m, 3H), 2.85-2.49 (m, 3H), 1.92-1.70(m, 4H).

Example 5: Synthesis of (2R,3S)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 205)

Step a: Synthesis of 3-O-Acetyl-1,2:5,6-di-O-isopropylidene-α-D-erythrohexofuran-3-enose

Acetic anhydride (65.77 mL) was added to a solution of compound (45 g), obtained from step a of Example 4, in pyridine (500 mL) and the reaction mixture was heated at 60°C for overnight. Reaction mixture was then concentrated to obtain a residue. Ethyl acetate and water were added to the residue. Organic layer was separated, washed with dilute hydrochloric acid, water and brine. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by silica gel column chromatography

using 8% ethyl acetate in hexane as eluant to furnish the title compound (21 g). Mass (m/z): 301.19(M^+ +1)

Step b: Synthesis of 3-O-acetyl-1,2:5,6-di-O-isopropylidene-α-D-gulofuranose

To a solution of compound (26 g), obtained from step a above, in ethyl acetate (250 mL), 10% Palladium on charcoal (6g) was added and the reaction mixture was shaken under hydrogen atmosphere at 60 psi for 4 hours on Paar apparatus. The reaction mixture was filtered through a celite bed. The solvents were evaporated to obtain a crude residue which was purified using column chromatography over silica gel using 15 % ethyl acetate in hexane as eluant to furnish the title compound (17 g). Mass (m/z): 324.97 (M^+ +Na)

Step c: Synthesis of 1,2:5,6-di-O-isopropylidene-α-D-gulofuranose

Sodium methoxide (12.5 g) was added to a solution of compound (64 g), obtained from step b above, in methanol (10 mL). The reaction mixture was stirred for 3 hours at 0°C. The reaction mixture was then concentrated. The residue thus obtained was purified by column chromatography over silica gel using 30 % ethyl acetate in hexane as eluant to afford the title compound (31 g). Mass (m/z): 261.26 (M^+ +1)

Step d: Synthesis of 1,2:5,6-di-O-isopropylidene-α-D-xylo-hexofuranos-3-ulose

Sodium hypochlorite (225 mL, 4% solution) was added dropwise to a solution compound (30 g), obtained from step c above, followed by addition of 2,2,6,6,-tetramethylpiperidine N-oxyl (0.18 g), potassium bromide (10.62 g) and sodium acetate (14.19 g) in ethyl acetate (300 mL) and water (100 mL). After 20 min, triethylamine (3.3 mL) was added dropwise to the above mixture at the same temperature. The reaction mixture was extracted with ethyl acetate after 30 min. The organic layer was dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure to afford the title compound (10.4 g).

Step e: Synthesis of 1,2:5,6-Di-O-isopropylidene- 3-deoxy-3-(2-ethoxy-2-oxoethylidene)- α-D-xylo-hexofuranose

To the solution of compound (10.5 g), obtained from step d above, in tetrahydrofuran, carboethoxymethylene triphenyl-phosphorane (27 g) was added. The reaction mixture was refluxed for 2 hours and concentrated to afford crude compound,

which was purified by column chromatography over silica gel using 8% ethyl acetate in hexane as eluant to yield the title compound (5.0 g). Mass (m/z): 350.28 (M^+ +Na)

Step f: Synthesis of 1,2:5,6-Di-O-isopropylidene- 3-deoxy-3-(2-ethoxy-2-oxoethyl)- α -D-gulofuranose

10% Palladium on charcoal (3 g) was added to the solution of compound (12 g), obtained from step e above, in methanol (50 mL) and the reaction mixture was stirred under hydrogen atmosphere at room temperature for 4 hours. The reaction mixture was filtered through a celite pad and the residue was washed using ethyl acetate. The filtrate was concentrated to furnish the title compound (12 g). Mass (m/z): 330.9 (M^+ +1).

Step g: Synthesis of 1,2:5,6-Di-O-isopropylidene-3-deoxy-3-(2-hydroxyethyl)-α -D-gulofuranose

To the suspension of lithium aluminium hydride (2.37 g) in tetrahydrofuran (120 mL) was added a solution of compound (12 g), obtained from step f above, in tetrahydrofuran (100 mL) at -50°C. The reaction mixture was allowed to attain the temperature 0°C and mixture was stirred for 30 minutes at 0°C. The reaction mixture was quenched using aqueous solution of ammonium chloride (25 mL). The reaction mixture was slowly allowed to attain the room temperature and further stirred for 12 hours at same temperature. The reaction mixture was filtered through a celite pad, residue was washed with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure to afford the title compound (8.5 g).

Step h: Synthesis of 1,2:5,6-Di-O-isopropylidene- 3-deoxy-3-[2-(1,3-dioxo1,3-dihydro-2H-isoindol-2-yl)ethyl]-α -D-gulofuranose

A mixture of compound (8.5 g), obtained from step g above, triphenyl phosphine (21.83g) and phthalimide (6.73 g) were taken in a round bottom flask and dried in high vacuum for 10 minutes. Then vacuum was released under a nitrogen atmosphere and tetrahydrofuran (100 mL) was added to the reaction mixture. The reaction mixture was cooled to 0°C and diisopropyl azodicarboxylate (12.625 g) was added slowly. The reaction mixture was stirred for 30 minutes at same temperature and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated. The residue thus

obtained was purified by column chromatography over silica gel using 40% ethyl acetate in hexane as eluant to afford the title compound (8.5 g).

Step i: Synthesis of 3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-1,2-O-(isopropylidene)-α-D-gulofuranose

30% Perchloric acid (8.15 mL) was added to a solution of compound (0.8 g) obtained from step h above, in tetrahydrofuran (200 mL). The reaction mixture was stirred for 2 hours at 0-5°C and then quenched with saturated solution of sodium hydrogen carbonate. Ethyl acetate and water were added to the resulting mixture. The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate and concentrated. The residue thus obtained was purified by column chromatography over silica gel using 60% ethyl acetate in hexane to afford 5.5 g of the title compound. Mass (m/z): 377.24 (M^+ +1)

Step j: Synthesis of (5R)-3-deoxy-3-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4,5-O-(1-methylethylidene)-L-arabino-pentodialdo-5,2-furanose

To a solution of compound (5.5 g), obtained from step i above, in acetone (100 mL) was added aqueous solution of sodium periodate (9.33 g in 100 mL) at 0°C. The reaction mixture was stirred for 2 hours, then filtered and concentrated. The residue thus obtained was taken in distilled water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated to afford the title compound (5.2 g).

Step k: Synthesis of 2-(2-{(3aR,5S,6R,6aR)-5-[(E)-2-(4-bromophenyl)ethenyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1H-isoindole-1,3(2H)-dione

A solution of (4-bromobenzyl)triphenylphosphonium bromide (13.3 g) in dimethyl sulphoxide (10 mL) was added dropwise to the suspension of sodium hydride (1 g of 50% suspension) in dimethyl sulphoxide (20 mL) at 0°C. After 20 minutes, a solution of compound (6 g), obtained from step j above, in dimethylsulphoxide (100 mL) was added dropwise and reaction mixture was stirred for 1 hour at the same temperature. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 40% ethyl acetate in hexane to furnish the title compound (5.5 g). Mass (m/z): 499.10 (M^+ +1)

Step l: Synthesis of 2-(2-{(3aR,5S,6R,6aR)-5-[(E)-2-(3'-fluoro-4'-methylbiphenyl-4-yl)ethenyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1H-isoindole-1,3(2H)-dione

A mixture of compound (0.5 g), obtained from step k above, 3-fluoro-4-methylphenylboronic acid (0.314 g), tetrakistriphenylphosphinepalladium (0) (0.057 g) and potassium carbonate (0.414 g) was dried under high vacuum for 10 minutes. The vacuum was released under nitrogen atmosphere and dry dimethylformamide (5 mL) was added at room temperature. The reaction mixture was heated at 120°C for 2 hours, and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 30% ethylacetate in hexane as eluant to afford the title compound (0.37 g). Mass (m/z): 527.23 (M^+ +1)

Step m: Synthesis of 2-(2-{(3aR,5S,6R,6aR)-5-[2-(3'-fluoro-4'-methylbiphenyl-4-yl)ethyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1H-isoindole-1,3(2H)-dione

10% Palladium on charcoal (100 g) was added to the solution of compound (0.37g), obtained from step l above, in ethyl acetate (10 mL) at room temperature and the reaction mixture was hydrogenated at the pressure of 35 psi for 1 hour in a Paar apparatus. The reaction mixture was filtered through celite pad and the residue was washed with methanol. The filtrate was concentrated to afford the title compound (0.28 g).

Step n: Synthesis of 2-(2-{(2S,3S,4R,5S)-2-[2-(3'-fluoro-4'-methylbiphenyl-4-yl)ethyl]-4,5-dihydroxytetrahydrofuran-3-yl}ethyl)-1H-isoindole-1,3(2H)-dione

To a solution of compound (0.28 g), obtained from step m above, in acetonitrile (20 mL) and water (2 mL) was added 30% perchloric acid (0.4 mL) at room temperature. The reaction mixture was heated to 55°C for 30 minutes. The reaction mixture was then quenched using sodium bicarbonate solution. The solvents were evaporated at reduced pressure. The residue thus obtained was taken in ethyl acetate and water. The organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was concentrated under the reduced pressure to yield the

title compound (0.418 g) as crude mass which was used further without any purification and characterization.

Step o: Synthesis of (2R,3S)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-(formyloxy)pentanoic acid

A solution of sodium metaperiodate (0.489 g in 5 mL of water) was added to a solution of compound (0.4 g), obtained from step n above, in a *tert*-butanol:tetrahydrofuran (5 mL: 5 mL) at 0°C. The reaction mixture was stirred for 2 hours at same temperature and potassium permangnate (0.033 g) was added at 0°C. After stirring, the reaction mixture for additional 6 hours at room temperature, the reaction mixture was evaporated on rotary evaporator, the residue was taken into water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure, to afford the title compound (0.31 g) as crude mass which was used further without any purification and characterization.

Step p: Synthesis of (2R,3S)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid

To a solution of compound (0.31g), obtained from step o above, in methanol (5 mL), potassium carbonate (0.094 g) was added at 0°C. The reaction mixture was stirred at room temperature for 3 hours. Reaction mixture was diluted with ethyl acetate (50 mL), acidified with sodium hydrogen sulphate and washed with water (20 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated under the reduced pressure obtain a residue which was purified by preparative thin layer chromatography using 10% methanol in dichloromethane as eluant to afford the title compound (0.020 g).
Mass (m/z): 476.07 (M^+ +1)

^{1}HNMR (CD_3OD): δ 7.72-7.64 (m, 4H), 7.36-7.34 (m, 2H), 7.18-7.10 (m, 5H), 3.68-3.61 (m, 3H), 2.75-2.71 (m, 1H), 2.55-2.49 (s, 1H), 2.32-2.30 (m, 1H), 2.16 (s, 3H), 1.99-1.94 (m, 2H), 1.70-1.62 (m, 2H).

Example 6: Synthesis of (2*S*,3*S*)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 208)

Step a: Synthesis of 5-O-[tert-butyl(diphenyl)silyl]-3-deoxy-1,2-O-isopropylidene-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]- α -L-ribofuranose

A mixture of compound (20 g), obtained from step f of Example 1, triphenyl phosphine (17.6 g) and 1,2,3-benzotriazin-4(3*H*)-one (7.2 g) were dried in high vacuum in a round bottom flask for 10 minutes. The vacuum was released under a nitrogen atmosphere and tetrahydrofuran (200 mL) was added to the above reaction mixture. The reaction mixture was cooled to 0°C and diisopropyl azodicarboxylate (9.8 mL) was added slowly. The reaction mixture was stirred for 30 minutes at same temperature, and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated to obtain a residue which was purified by column chromatography over silica gel using 30% ethylacetate in hexane as eluant to afford the title compound (22 g). Mass (m/z): 586.24 (M^+ +1).

Step b: Synthesis of 3-deoxy-1,2-O-isopropylidene-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]- α -L-ribofuranose

To a solution of compound (22 g), obtained from step a above, in dry tetrahydrofuran (200 mL) at 0°C, was added 1 M solution of tetra-butylammonium fluoride (75 mL). The resulting mixture was initially stirred at the 0°C for 1 hour and then at room temperature for 4 hours. The reaction mixture was cooled to 0°C, quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulphate and concentrated. The residue thus obtained was purified by column chromatography over silica gel using 50% ethyl acetate in hexane as eluant to furnish the title compound (6.5 g). Mass (m/z): 348.25(M^+ +1)

Step c: Synthesis of (5S)-3-deoxy-4,5-O-isopropylidene-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-D-ribo-pentodialdo-5,2-furanose

To the solution of compound (6.5 g), obtained from step b above, in dry dichloromethane (100 mL), cooled to 0°C, was added Dess-Martin periodinane reagent (11.1 g). The reaction mixture was allowed to stir for 2 hours. The reaction mixture was quenched with sodium thiosulphate and sodium hydrogen carbonate. Dichloromethane

was added to the reaction mixture. Organic layer was separated, washed with water and brine solution, dried over sodium sulphate and evaporated to afford the title compound. (6.5g)

Step d: Synthesis of 3-(2-{(3aS,5S,6S,6aS)-5-[(E)-2-(4-bromophenyl)vinyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one

To the suspension of sodium hydride (0. 979 g, 60% in oil) in dimethyl sulphoxide (60 mL), cooled to 0℃, was added (4-bromobenzyl)triphenylphosphonium bromide (14.5 g). Compound (6.5 g), obtained from step c above, in tetrahydrofuran (60 mL) was added dropwise after 20 minutes, and reaction mixture was stirred for 1 hour at the same temperature. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure and the residue thus obtained was purified by column chromatography using 40 % ethyl acetate in hexane as eluant to furnish the title compound (4 g). Mass (m/z): 498.19(M^+ +1)

Step e: Synthesis of 3-(2-{(3aS,5S,6S,6aS)-5-[(E)-2-(4'-methoxybiphenyl-4-yl)vinyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one

A mixture of compound (1g), obtained from step d above, 4-methoxyphenyl boronic acid (0.61 g), tetrakistriphenylphosphine palladium (0) (0.232 g) and potassium carbonate (0.832 g) was dried under high vacuum for 10 minutes and dry dimethylformamide (20 mL) was added at room temperature. The reaction mixture was heated at 120°C for 2 hours, and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 50% ethyl acetate in hexane as eluant to afford the title compound (0.62 g). Mass (m/z): 526.41(M^+ +1)

Step f: Synthesis of 3-(2-{(3aS,5S,6S,6aS)-5-[2-(4'-methoxybiphenyl-4-yl)ethyl]-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one

To the solution of compound (0.62 g), obtained from step e above, in a solvent mixture of ethyl acetate (20 mL) was added 10% Palladium on charcoal (0.3 g) at room temperature and the reaction mixture was hydrogenated at the pressure of 35 psi for 4 hours in a Paar apparatus. The reaction mixture was filtered through a celite pad and the residue was washed with methanol. The filtrate was concentrated to afford the title compound (0.6 g).

Step g: Synthesis 3-(2-{(2S,3R,4S,5R)-4,5-dihydroxy-2-[2-(4'-methoxybiphenyl-4-yl)ethyl]tetrahydrofuran-3-yl}ethyl)-1,2,3-benzotriazin-4(3H)-one

Perchloric acid (0.2 mL) was added to a solution of compound (0.6 g), obtained from step f above, in acetonitrile (50 mL) and water (10 mL) at room temperature. The reaction mixture was heated to 55°C for 30 minutes. The reaction mixture was then quenched using sodium hydrogen carbonate solution. The solvents were evaporated at reduced pressure. The residue thus obtained was taken in ethyl acetate and water. The organic layer was separated and washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was concentrated under the reduced pressure to yield the title compound (0.6 g).

Step h: Synthesis of (2S,3S)-3-(formyloxy)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4-pyrimidin-5-ylphenyl)pentanoic acid

To a solution of compound (0.6 g), obtained from step g above, in a *tert*-butanol:tetrahydrofuran (7 mL: 7 mL) at 0°C was added a solution of sodium metaperiodate (0.973 g in 7 mL of water). The reaction mixture was stirred for 2 hours at same temperature and potassium permangnate (0.036 g) was added at 0°C. After stirring the reaction mixture for an additional 6 hours at room temperature, reaction mixture was evaporated, the residue was taken into water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure, to afford the title compound (0.5 g).

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

Potassium carbonate (0.151 g) was added to a solution of compound (0.5 g), obtained from step h above, in methanol (5 mL) and tetrahydrofuran (5 mL) at 0°C. The

reaction mixture was stirred at room temperature for 3h. Solvents were evaporated and the residue was taken into water and ethyl acetate. Organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. Solvent was evaporated under the reduced pressure obtain a residue which was purified by preperative thin layer chromatography using 10% methanol in dichloromethane as eluent to afford the title compound (0.008g). Mass (m/z): 474.31 (M^+ +1); ^{1}HNMR (CD_3OD): δ 8.32-7.87 (m, 5H), 7.50-7.42 (m, 4H), 7.24-7.20 (m, 2H), 6.97-6.94 (m, 1H), 4.60-4.50 (m, 2H), 3.81 (s, 3H), 3.59 (br t, 1H), 3.0-1.8 (m, 7H).

Example 7: Synthesis of (2*S*,3*R*)-3-hydroxy-5-[4-(5-methylpyridin-2-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 209)

Step a: Synthesis of 4-(5-methylpyridin-2-yl)benzaldehyde

A mixture of 2-bromo-5-methylpyridine (2g), (4-formylphenyl)boronic acid (3.5 g), tetrakistriphenylphosphinepalladium (0) (0.672 g) and potassium carbonate (4.8 g) was dried under high vacuum for 10 minutes and dry dimethylformamide (15 mL) was added at room temperature. The reaction mixture was heated at 110°C for 6 hours, and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under the reduced pressure to obtain a residue which was purified by column chromatography over silica gel using 20% ethylacetate in hexane as eluant to afford the title compound (2.8 g). Mass (m/z): 198.20

Step b: Synthesis of ethyl (2E)-3-[4-(5-methylpyridin-2-yl)phenyl]prop-2-enoate

To the suspension of sodium hydride (0.682 g, 60% in oil.) in tetrahydrofuran (20 mL) at 0℃ was charged triethyl phosphonoacetate (3.82 g). After 15 minutes, a solution of compound (2.8 g), obtained from step a above, in tetrahydrofuran (5mL) was added dropwise and the reaction mixture was stirred for 30 minutes at room temperature. A saturated solution of ammonium chloride in water was added to reaction mixture. The solvent was evaporated and the resulting mixture was extracted with ethyl acetate. The combined extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure to yield a residue which was purified by column chromatography over silica gel using 15% ethylacetate in hexane as eluant to afford the title compound (1.8 g).

Step c: Synthesis of ethyl 3-[4-(5-methylpyridin-2-yl)phenyl]propanoate

10% Palladium on charcoal (0.8 g) was added to the solution of compound (1.8 g), obtained from step b above, in tetrahydrofuran (15 mL) at room temperature and hydrogen was supplied at the pressure of 50 psi (Paar apparatus) for 4 hours. The reaction mixture was filtered through celite pad and concentrated to afford the title compound (1.8 g).

Step d: Synthesis of 3-[4-(5-methylpyridin-2-yl)phenyl]propan-1-ol

To the suspension of lithium aluminium hydride (0.424 g) in tetrahydrofuran (20 mL) was added a solution of compound (2 g), obtained from step c above, in tetrahydrofuran (10 mL) at -20°C. The reaction mixture was stirred for 2 hours at –30°C and saturated solution of sodium sulphate was added at the same temperature. The reaction mixture was then filtered through a celite pad and the residue was washed with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered, concentrated under reduced pressure and the residue thus obtained was purified by column chromatography over silica gel using 50% ethylacetate in hexane as eluant to afford the title compound (1.2 g).

Step e: Synthesis of 3-[4-(5-methylpyridin-2-yl)phenyl]propanal

To a stirred solution of compound (1.4g), obtained from step d above, in dichloromethane (20 mL), 2,2,6,6,-tetramethylpiperidine N-oxyl (9.6 mg), and potassium bromide (73.4 mg) was added at 0°C under nitrogen atmosphere. Sodium hypochlorite (13.7 mL, 4% solution) was added at once at pH 8-9 (maintained by adding aqueous sodium bicarbonate solution). The reaction was stirred for 20 min at 0^0C. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution, water and brine. The organic layer was dried over anhydrous sodium sulphate, filtered, concentrated under reduced pressure to afford crude aldehyde (0.9 g).

Step f: Synthesis of 3-{(3S,4R)-3-{[(4S)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl}-4-hydroxy-6-[4-(5-methylpyridin-2-yl)phenyl]hexyl}-1,2,3-benzotriazin-4(3H)-one

In a flame-dried flask, 3-{4-[(4S)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-4-oxobutyl}-1,2,3-benzotriazin-4(3H)-one (1.18 g) was taken up in dichloromethane (10 mL) and cooled to 0°C. Titanium tetrachloride (3.4 mL) in dichloromethane (6 mL) was added dropwise and reaction mixture was stirred for 10-15 minutes. (-)-Sparteine (1.7 g)

was added slowly to the reaction mixture and stirred at 0℃ for 45 minutes. A solution of compound (0.65 g), obtained from step e above, in dichloromethane (10 mL) was added slowly and stirring was continued at 0℃. After 3 hours, the reaction was quenched with dropwise addition of saturated ammonium chloride solution and dichloromethane was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layer was washed with brine, and dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude product thus obtained was purified by silica gel flash column chromatography using 30% ethyl acetate in hexanes as eluant to afford the aldol adduct (0.56 g).

Step g: Synthesis of (2S,3R)-3-hydroxy-5-[4-(5-methylpyridin-2-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid

To a stirred solution of the compound (0.2 g), obtained from step f above, in tetrahydrofuran: water (3:1, 10 mL) at 0℃ was added aqueous hydrogen peroxide solution (30%, 0.16 mL), followed by addition of lithium hydroxide monohydrate (0.02g) in water (5 mL). The reaction mixture was stirred at 0℃ for 30 minutes. The reaction mixture was concentrated and the residue was extracted with ethyl acetate. The aqueous layer was acidified with sodium hydrogen sulphate and extracted with ethyl acetate. The combined layers were washed with water, brine and dried over anhydrous sodium sulphate. The solvents were evaporated under reduced pressure and the crude residue was purified by silica gel flash column chromatography using 3% methanol in dichloromethane as eluant to afford the title compound (0.035 g). Mass (m/z): 459.21(M^+ +1); ^{1}HNMR (CD_3OD): δ 8.40 (s, 1H), 8.30 (d, 1H, J = 7.88 Hz), 8.15 (d, 1H, J = 8Hz), 8.05-7.70 (m, 6H), 7.27 (d, 2H, J = 7.6 Hz), 4.40-4.0 (m, 2H), 3.80-3.60 (m, 1H), 2.80-2.40 (m, 5H), 2.38(s, 3H), 1.80-1.60 (m, 2H).

Example 7A: Synthesis of (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. 86)

Step a: Synthesis of methyl (2*E*)-3-(4-bromophenyl)prop-2-enoate

To a stirred solution of 4-bromocinnamic acid (16g) in methanol (150 mL) was added thionyl chloride (30 mL) at 0℃. The reaction mixture was warmed to room temperature and refluxed for 3 hours. After cooling to room temperature the solvents were evaporated to dryness. The crude compound obtained was used as such for the next step.

Step b: Synthesis of methyl (2*E*)-3-[4-(6-methoxypyridin-3-yl)phenyl]prop-2-enoate

Compound (7.5 g) obtained from step a above, pyridine-2-methoxy-5-boronic acid (9.48 g), tetrakistriphenylphosphinepalladium (0) (1.79 g) and potassium carbonate (12.83 g) were taken in dimethylformamide (60 mL) under nitrogen atmosphere. The reaction mixture was refluxed under nitrogen atmosphere for 6 hours. After cooling to room temperature, water was added and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and the solvents were evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography using 20-30 % ethyl acetate in hexane to get the title compound (8.09 g).

Step c: Synthesis of methyl 3-[4-(6-methoxypyridin-3-yl)phenyl]propanoate

To the solution of compound (8.1 g), obtained from step b above, in a mixture of ethyl acetate /methanol /tetrahydrofuran (~300 mL), 10% Palladium on charcoal (1.6 g) was added and stirred under hydrogen atmosphere at the pressure of 30 psi (Paar apparatus) for 2.5 hours. The reaction mixture was filtered through celite pad washed with ethyl acetate and the filtrate was concentrated under reduced pressure to obtain the title compound as white solid which was used as such for the next step.

Step d: Synthesis of 3-[4-(6-methoxypyridin-3-yl)phenyl]propanoic acid

To a stirred solution of lithium aluminium hydride (2.28 g) in tetrahydrofuran (120 mL) was added the compound (8g), obtained from step c above in tetrahydrofuran (50 mL) at 0℃. The reaction mixture was stirred at 0℃ for 3 hours. The reaction mixture was quenched carefully with saturated ammonium chloride solution, filtered through celite, washed with ethyl acetate. The organic layers were separated, washed with brine and dried over anhydrous sodium sulfate and solvents were evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography using 20-30 % ethyl acetate in hexane to get the title compound as a white crystalline solid (5.1 g).

Step e: Synthesis of 3-[4-(6-methoxypyridin-3-yl)phenyl]propanal

To a stirred solution of compound (9.0 g) obtained from step d above, in dichloromethane (90 ml), 2,2,6,6,-tetramethylpiperidine N-oxyl (58.77 mg) and potassium bromide (447.57 mg) was added at 0℃ under nitrogen atmosphere. A 4% aqueous sodium hypochlorite (3.497 g) was added at once at pH 8-9 (maintained by adding

saturated aqueous sodium bicarbonate solution). The reaction was stirred for 20 minutes at 0 °C. Then, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution, water and brine. Finally, the organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude aldehyde (8.1g) which was used as such in the next step.

Step f: Synthesis of 3-{(3*S*,4*S*)-3-{[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl}-4-hydroxy-6-[4-(5-methoxypyridin-2-yl)phenyl]hexyl}-1,2,3-benzotriazin-4(3*H*)-one

In a flame-dried flask, 3-{4-[(4S)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-4-oxobutyl}-1,2,3-benzotriazin-4(3H)-one (2.0 g) was taken up in dichloromethane (10 mL) and cooled to 0 °C. Titanium tetrachloride (0.619 mL) in dichloromethane (6 mL) was added dropwise and reaction mixture was stirred for 10-15 minutes. (-)-Sparteine (2.7 mL) was added slowly to the reaction mixture and stirred at 0 °C for 45 minutes. A solution of compound (1.34 g), obtained from step e above, in dichloromethane (10 mL) was added slowly and stirring was continued at 0^0C. After 3 hours, the reaction was quenched with dropwise addition of saturated ammonium chloride solution and dichloromethane was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layer was washed with brine, and dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude product thus obtained was purified by silica gel flash column chromatography using 30% ethyl acetate in hexanes as eluants to afford the aldol adduct (1.21g).

Step g: Synthesis of (2*S*,3*R*)-3-hydroxy-5-[4-(5-methoxypyridin-2-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid

To a stirred solution of the compound (1.21 g), obtained from step f above, in tetrahydrofuran: water (3:1, 15 mL) at 0 °C was added aqueous hydrogen peroxide solution (30%, 1.02 mL), followed by addition of lithium hydroxide monohydrate (114.5mg) in water (5 mL). The reaction mixture was stirred at 0 °C until the completion of the hydrolysis. The reaction mixture was concentrated and the residue was extracted with ethyl acetate. The aqueous layer was acidified with sodium hydrogen sulphate and extracted with ethyl acetate. The combined layers were washed with water, brine and dried over anhydrous sodium sulphate. The solvents were evaporated under reduced

pressure and the crude residue was purified by silica gel flash column chromatography using 3% methanol in dichloromethane as eluant to afford the title compound (0.61 g). Mass (m/z): 474.87(M^+ +1); ^{1}H NMR (400 MHz, MeOD): δ 8.32- 8.30 (2H, m), 8.16- 8.14 (1H, m), 8.04- 8.03 (1H, m), 7.92- 7.88 (2H, m), 7.46 (2H, d, J = 8Hz), 7.24 (2H, m, J = 8Hz), 6.86 (1H, d, J = 8Hz), 4.57- 4.53 (2H, m), 3.93 (3H, s), 3.78-3.83 (1H, m), 2.83- 2.80 (1H, m), 2.63- 2.60 (1H, m), 2.52- 2.49 (1H, m), 2.32- 2.28 (2H, m), 1.80- 1.76 (2H, m).

Example 7B: Synthesis of (2*S*,3*R*)-5-(2',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 216)

Step a: Synthesis of methyl (2*E*)-3-(4-bromophenyl)prop-2-enoate

To a stirred solution of 4-bromocinnamic acid (16g) in methanol (150 mL) was added thionyl chloride (30 mL) at 0℃. The reaction mixture was warmed to room temperature and refluxed for 3 hours. After cooling to room temperature the solvents were evaporated to dryness. The crude compound obtained was used as such for the next step.

Step b: Synthesis of methyl (2*E*)-3-(3',5'-difluorobiphenyl-4-yl)prop-2-enoate

Compound (0.75 g) obtained from step a above, 2,4difluorophenyl boronic acid (0.737 g), tetrakistriphenylphosphinepalladium (0) (0.07 g) and potassium carbonate (1.28 g) were taken in dimethylformamide (6 mL) under nitrogen atmosphere. The reaction mixture was refluxed under nitrogen atmosphere for 6 hours. After cooling to room temperature, water was added and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and the solvents were evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography using 20-30 % ethyl acetate in hexane to get the title compound (0.810 g).

Step c: Synthesis of methyl 3-(3',5'-difluorobiphenyl-4-yl)propanoate

To the solution of compound (0.79 g), obtained from step b above, in a mixture of ethyl acetate (~10 mL), 10% Palladium on charcoal (0.2g) was added and stirred under hydrogen atmosphere at the pressure of 30 psi for 2.5 hours. The reaction mixture was filtered through celite pad washed with ethyl acetate and the filtrate was concentrated under reduced pressure to obtain the title compound (0.77g) as white solid which was used as such for the next step.

Step d: Synthesis of 3-(3',5'-difluorobiphenyl-4-yl)propanoic acid

To a stirred solution of lithium aluminium hydride (0.2 g) in tetrahydrofuran (15 mL) was added the compound (0.77g), obtained from step c above in tetrahydrofuran (50 mL) at 0 ℃ .The reaction mixture was stirred at 0 ℃ for 3 hours. The reaction mixture was quenched carefully with saturated ammonium chloride solution, filtered through celite, washed with ethyl acetate. The organic layers were separated, washed with brine and dried over anhydrous sodium sulfate and solvents were evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography using 20-30 % ethyl acetate in hexane to get the title compound as a white crystalline solid (0.70 g).

Step e: Synthesis of 3-(3',5'-difluorobiphenyl-4-yl)propanal

To a stirred solution of compound (0.7g), obtained from step d above, in dichloromethane (10 mL), 2,2,6,6,-tetramethylpiperidine N-oxyl (4.36 mg), and potassium bromide (33.32 mg) was added at 0 ℃ under nitrogen atmosphere. Sodium hypochlorite (6.5mL, 4% solution) was added at once at pH 8-9 (maintained by adding aqueous sodium bicarbonate solution). The reaction was stirred for 20 min at 0 ℃. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution, water and brine. The organic layer was dried over anhydrous sodium sulphate, filtered, concentrated under reduced pressure to afford crude aldehyde (0.57 g).

Step f: Synthesis of 3-[(2*R*,3*S*)-2-{[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl}-5-(3',5'-difluorobiphenyl-4-yl)-3-hydroxypentyl]-1,2,3-benzotriazin-4(3*H*)-one

In a flame-dried flask, 3-{3-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-3-oxopropyl}-1,2,3-benzotriazin-4(3*H*)-one (0.25 g) was taken up in dichloromethane (10 mL) and cooled to 0 ℃. Titanium tetrachloride (0.76 mL, 1M solution) was added dropwise and reaction mixture was stirred for 10-15 minutes. (-)-Sparteine (0.36 mL) was added slowly to the reaction mixture and stirred at 0 ℃ for 20 minutes. A solution of compound (0.187 g), obtained from step e above, in dichloromethane (10 mL) was added slowly and stirring was continued at 0 ℃. After 3 hours, the reaction was quenched with dropwise addition of saturated ammonium chloride solution and dichloromethane was added. The organic layer was separated and the aqueous layer was extracted with

dichloromethane. The organic layer was washed with brine, and dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude product thus obtained was purified by silica gel flash column chromatography using 30% ethyl acetate in hexane as eluants to afford the aldol adduct (0.24g).

Step g: Synthesis of (2*S*,3*R*)-5-(3',5'-difluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid

To a stirred solution of the compound (0.2g), obtained from step f above, in tetrahydrofuran: water (3:1, 10 mL) at 0°C was added aqueous hydrogen peroxide solution (30%, 0.16 mL), followed by addition of lithium hydroxide monohydrate (19.53mg) in water (2 mL). The reaction mixture was stirred at 0°C until the completion of the hydrolysis. The reaction mixture was concentrated and the residue was extracted with ethyl acetate. The aqueous layer was acidified with sodium hydrogen sulphate and extracted with ethyl acetate. The combined layers were washed with water, brine and dried over anhydrous sodium sulphate. The solvents were evaporated under reduced pressure and the crude residue was purified by silica gel flash column chromatography using 10% methanol in dichloromethane as eluant to afford the title compound (0.090g). Mass (m/z): 466.06 (M^+ +1); ^{1}HNMR (CD_3OD): δ 8.17-8.8.15 (m, 1H), 8.05-8.01(m, 1H), 7.90-7.88 (m, 1H), 7.86-7.84 (m, 1H), 7.46-7.42 (m, 2H,), 7.40-7.29 (m, 2H,), 7.03-6.98 (m, 2H), 4.82-4.84 (m, 2H), 3.94 (s, 1H), 3.22 – 3.21 (m, 1H), 2.91-2.89 (m, 1H), 2.78-2.75 (m, 1H), 1.94-1.90 (m, 2H).

Example 7C: Synthesis of (2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 217)

Step a: Synthesis of methyl (2*E*)-3-(4-bromophenyl)prop-2-enoate

To a stirred solution of 4-bromocinnamic acid (16g) in methanol (150 mL) was added thionyl chloride (30 mL) at 0°C. The reaction mixture was warmed to room temperature and refluxed for 3 hours. After cooling to room temperature the solvents were evaporated to dryness. The crude compound obtained was used as such for the next step.

Step b: Synthesis of methyl (2*E*)-3-(4'-fluorobiphenyl-4-yl)prop-2-enoate

Compound (0.75 g) obtained from step a above, 4-fluorophenyl boronic acid (0.65 g), tetrakistriphenylphosphinepalladium (0) (0.07 g) and potassium carbonate (1.28 g) were taken in dimethylformamide (6 mL) under nitrogen atmosphere. The reaction

mixture was refluxed under nitrogen atmosphere for 6 hours. After cooling to room temperature, water was added and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and the solvents were evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography using 20-30 % ethyl acetate in hexane to get the title compound (0.720 g).

Step c: Synthesis of methyl 3-(4'-fluorobiphenyl-4-yl) propanoate

To the solution of compound (0.7 g), obtained from step b above, in a mixture of ethyl acetate (~20 mL), 10% Palladium on charcoal (0.2 g) was added and stirred under hydrogen atmosphere at the pressure of 30 psi (Paar apparatus) for 2.5 hours. The reaction mixture was filtered through celite pad washed with ethyl acetate and the filtrate was concentrated under reduced pressure to obtain the title compound (0.7g) as white solid which was used as such for the next step.

Step d: Synthesis of 3-(4'-fluorobiphenyl-4-yl)propanoic acid

To a stirred solution of lithium aluminium hydride (0.2 g) in tetrahydrofuran (15 mL) was added the compound (0.7g), obtained from step c above in tetrahydrofuran (50 mL) at 0℃ .The reaction mixture was stirred at 0℃ for 3 hours. The reaction mixture was quenched carefully with saturated ammonium chloride solution, filtered through celite, washed with ethyl acetate. The organic layers were separated, washed with brine and dried over anhydrous sodium sulfate and solvents were evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography using 20-30 % ethyl acetate in hexane to get the title compound as a white crystalline solid (0.70 g).

Step e: Synthesis of 3-(4'-fluorobiphenyl-4-yl) propanal

To a stirred solution of compound (0.7g), obtained from step d above, in dichloromethane (10 mL), 2,2,6,6,-tetramethylpiperidine N-oxyl (4.74 mg), and potassium bromide (36.05 mg) was added at 0℃ under nitrogen atmosphere. Sodium hypochlorite (0.28g, 4% solution) was added at once at pH 8-9 (maintained by adding aqueous sodium bicarbonate solution). The reaction was stirred for 20 min at 0℃. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate

solution, water and brine. The organic layer was dried over anhydrous sodium sulphate, filtered, concentrated under reduced pressure to afford crude aldehyde (0.55 g).

Step f: Synthesis of 3-[(2*R*,3*S*)-2-{[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]carbonyl}-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentyl]-1,2,3-benzotriazin-4(3*H*)-one

In a flame-dried flask, 3-{3-[(4*S*)-4-benzyl-2-oxo-1,3-thiazolidin-3-yl]-3-oxopropyl}-1,2,3-benzotriazin-4(3*H*)-one (0.25 g) was taken up in dichloromethane (10 mL) and cooled to 0°C. Titanium tetrachloride (0.76 mL, 1M solution) was added dropwise and reaction mixture was stirred for 10-15 minutes. (-)-Sparteine (0.36 mL) was added slowly to the reaction mixture and stirred at 0°C for 20 minutes. A solution of compound (0.17 g), obtained from step e above, in dichloromethane (10 mL) was added slowly and stirring was continued at 0°C. After 3 hours, the reaction was quenched with dropwise addition of saturated ammonium chloride solution and dichloromethane was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layer was washed with brine, and dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude product thus obtained was purified by silica gel flash column chromatography using 30% ethyl acetate in hexanes as eluants to afford the aldol adduct (0.2g).

Step g: Synthesis of (2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid

To a stirred solution of the compound (0.18 g), obtained from step f above, in tetrahydrofuran: water (3:1, 10 mL) at 0°C was added aqueous hydrogen peroxide solution (30%, 0.15 mL), followed by addition of lithium hydroxide monohydrate (17.6mg) in water (2 mL). The reaction mixture was stirred at 0°C until the completion of the hydrolysis. The reaction mixture was concentrated and the residue was extracted with ethyl acetate. The aqueous layer was acidified with sodium hydrogen sulphate and extracted with ethyl acetate. The combined layers were washed with water, brine and dried over anhydrous sodium sulphate. The solvents were evaporated under reduced pressure and the crude residue was purified by silica gel flash column chromatography using 10% methanol in dichloromethane as eluant to afford the title compound (0.075 g). Mass (m/z): 448.07 (M^+ +1); ^{1}HNMR (CD_3OD): δ 8.25-8.8.30 (d, 1H, J = 8Hz), 8.15-8.12 (d, 1H, J = 8Hz), 8.05-8.00 (t, 1H, J = 8Hz), 7.89-7.85 (t, 1H, J = 8Hz), 7.58-7.55 (m,

1H,), 7.47-7.45 (d, 1H J = 8Hz), 7.28- 7.26 (d, 1H, J = 8Hz), 7.89-7.87 (m, 1H), 7.61 (m, 2H), 7.53- 7.59 (m,1H), 7.30-7.25 (d, 2H J = 8Hz), 7.15- 7.11 (t, 2H, J = 8Hz), 4.81-4.79 (m, 2H), 3.92 (s, 1H), 3.22–3.16 (m, 1H), 2.92- 2.90 (m, 1H), 2.75- 2.73 (m, 1H), 1.93-1.87 (m, 2H).

The following compounds were prepared employing procedures as provided in Examples 1 to 7C described above:

Compound Nos. 1 to 81, 86-88, 90-95, 97-119, 121-142, 144-203, 211-213 and 226-232 were prepared following Example 1; compound Nos. 82-83 were prepared following Example 2; compound Nos 84–85, and 204 were prepared following Example 3; compound Nos. 89 and 96 were prepared following Example 4; compound Nos 120, and 205-207 were prepared following Example 5; compound Nos. 143 and 208 were prepared following Example 6; and compound Nos 86, 209-210 and 214-225 were prepared following Example 7.

Specific compounds, suitable for use, prepared in the present invention, are listed below:

(2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4-pyrimidin-5-ylphenyl)pentanoic acid (Compound No.1), Mass (m/z):446.0 (M^+ +1);

(2S,3R)-2-[2-(5-tert-butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 2), Mass (m/z): 531.09 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 3), Mass (m/z): 458.82(M^+ +1);

(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. 4),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 5), Mass (m/z): 479.70(M^+ +1);

(2S,3R)-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 6), Mass (m/z):458.94 (M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 7), Mass (m/z): 472.87 (M^+ +1);

(2S,3R)-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. 8),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 9), Mass (m/z):461.87 (M^+ +1);

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 10), Mass (m/z):473.79 (M^+ +1);

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 11), Mass (m/z):493.81 (M^+ +1);

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 12), Mass (m/z): 479.77(M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 13), Mass (m/z):473.86 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 14), Mass (m/z):510.66 (M^+ -18);

(2S,3R)-5-(4'-chloro-3'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 15), Mass (m/z):496.10 (M^+ +1);

(2S,3R)-2-[2-(5-tert-butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 16), Mass (m/z):536.11 (M^+ +1);

(2S,3R)-2-[2-(5-tert-butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 17), Mass (m/z):530.09 (M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 18), Mass (m/z): 512.04(M^+ +1);

(2S,3R)-2-[2-(5-tert-butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 19), Mass (m/z):518.14 (M^+ +1);

(2S,3R)-2-[2-(5-tert-butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 20), Mass (m/z):534.09 (M^+);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 21), Mass (m/z):512.08 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 22), Mass (m/z): 458.14(M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 23), Mass (m/z): 492.07(M^+ +1);

(2S,3R)-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. 24), Mass (m/z):489.11 (M^+ +1);

(2S,3R)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 25), Mass (m/z):458.14 (M^+ +1);

(2S,3R)-5-(4'-ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 26), Mass (m/z): 472.15(M^+ +1);

(2S,3R)-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. 27), Mass (m/z):492.08 (M^+ +1);

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 28), Mass (m/z):478.09 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyrimidin-5-ylphenyl)pentanoic acid (Compound No. 29), Mass (m/z):446.12 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 30), Mass (m/z): 448.25 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyridin-3-ylphenyl)pentanoic acid (Compound No. 31), Mass (m/z): 445.23(M^+ +1);

(2S,3R)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 32), Mass (m/z):502.19 (M^+ +1);

(2S,3R)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 33), Mass (m/z):489.0(M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 34), Mass (m/z):473.0(M^+ +1);

(2S,3R)-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 35), Mass (m/z): 448.0 (M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 36), Mass (m/z): 505.0 (M^+ +1);

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 37), Mass (m/z):509.0 (M^+ +1);

(2S,3R)-3-hydroxy-2-{2-[7-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 38), Mass (m/z):582.0 (M^+ +1);

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 39), Mass (m/z): 511.0 (M^+ +1);

(2*S*,3*R*)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid(Compound No. 40), Mass (m/z): 493.3(M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 41), Mass (m/z):489.0 (M^+ +1);

(2S,3R)-3-hydroxy-2-{2-[5-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 42), Mass (m/z): 582.0(M^+ +1);

(2S,3R)-5-(4'-chloro-3'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 43), Mass (m/z):519.0 (M^+ +23);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-isobutyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 44), Mass (m/z):490.0 (M^+ +1);

(2S,3R)-5-biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 45), Mass (m/z): 444.0 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 46), Mass (m/z):476.0 (M^+ +1);

(2S,3R)-5-(3,3'-difluoro-4'-methoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 47), Mass (m/z):510.0 (M^+ +1);

(2S,3R)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 48), Mass (m/z):502.0 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1H-tetrazol-1-yl)phenyl]pentanoic acid (Compound No. 49), Mass (m/z): 458.0 (M^+ +23);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 50), Mass (m/z):493.0 (M^+ +1);

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 51), Mass (m/z): 498.0 (M^+ +23);

(2S,3R)-3-hydroxy-5-[4-(1-isobutyl-1H-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 52), Mass (m/z):490.0 (M^+ +1);

(2S,3R)-5-biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 53), Mass (m/z):444.0 (M^+ +1);

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 54), Mass (m/z): 489.34(M^+ +1)

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 55), Mass (m/z): 493.16(M^+ +1);

(2S,3R)-5-(4'-chloro-3-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 56), Mass (m/z): 496.13 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[6-(4-methoxyphenyl)pyridin-3-yl]pentanoic acid (Compound No. 57), Mass (m/z): 475.13 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 58), Mass (m/z): 492.13 (M^+ +1);

(2S,3R)-5-[6-(4-chlorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 59), Mass (m/z):479.12 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 60), Mass (m/z): 476.16 (M^+ +1);

(2S,3R)-5-[4-(4-chlorophenyl)-2-thienyl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 61), Mass (m/z):484.0 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)-2-thienyl]pentanoic acid (Compound No. 62), Mass (m/z): 481.0(M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-{4-[4-(trifluoromethyl)phenyl]-2-thienyl}pentanoic acid (Compound No. 63), Mass (m/z):518.0 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[4-(3-fluoro-4-methoxyphenyl)-2-thienyl]-3-hydroxypentanoic acid (Compound No. 64), Mass (m/z): 498.0 (M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 65), Mass (m/z):526.0 (M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 66), Mass (m/z):526.0 (M^+ +1);

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 67), Mass (m/z): 492.0(M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 68), Mass (m/z): 542.29(M^+ +1);

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 69), Mass (m/z):548.54 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[2-fluoro-5-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 70), Mass (m/z): 493.30(M^+ +1);

(2S,3R)-5-(4'-chloro-4-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 71), Mass (m/z):495.72 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[6-fluoro-4'-(trifluoromethyl)biphenyl-3-yl]-3-hydroxypentanoic acid (Compound No. 72), Mass (m/z):530.13 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[4-fluoro-3-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 73), Mass (m/z):493.37 (M^+ +1);

(2S,3R)-5-(4'-chloro-6-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 74), Mass (m/z):496.26 (M^+ +1);

(2S,3R)-5-(3',6-difluoro-4'-methoxybiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 75), Mass (m/z):509.77 (M^+ +1);

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 76), Mass (m/z): 492.56(M^+ +1);

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 77), Mass (m/z):480.0 (M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 78), Mass (m/z): 462.19 (M^+ +1);

(2S,3R)-2-[2-(5-chloro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 79), Mass (m/z):546.32 (M^+ +1);

(2S,3R)-2-[2-(4-fluoro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 80), Mass (m/z):529.25 (M^+ +1);

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 81), Mass (m/z): 498.27(M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid (Compound No. 82); Mass (m/z):368.0 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-phenylpentanoic acid (Compound No. 83), Mass (m/z): 368.07 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4 (trifluoromethyl)phenyl]pentanoic acid (Compound No.84), Mass (m/z): 458.0(M^+ +23);

(2S,3R)-5-(4-tert-butylphenyl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.85), Mass (m/z):424.0 (M^+ +1);

(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. 86), Mass (m/z): 474.87(M^+ +1);

(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. 87), Mass (m/z): 478.09(M^+ +1);

(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.88), Mass (m/z): 474.88(M^+ +1);

(2R,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 89), Mass (m/z):478.2 (M^+ +1);

(2*S*,3*R*)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 90), Mass (m/z): 462.32(M^+ +1);

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 91), Mass (m/z): 478.38(M^+ +1);

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 92), Mass (m/z): 514.20(M^+ +1);

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 93), Mass (m/z): 508.29(M^+ +1);

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 94),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 95), Mass (m/z): 493.37(M^+ +1);

(2*R*,3*R*)-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. 96), Mass (m/z): 474.87(M^+ +1);

(2S,3R)-5-(2',4'-difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 97), Mass (m/z): 480.13(M^+ +1);

(2S,3R)-2-[2-(6-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 98), Mass (m/z): 482.15 (M^+ +1);

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 99), Mass (m/z): 482.15(M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-isopropylbiphenyl-4-yl)pentanoic acid (Compound No. 100), Mass (m/z): 486.18(M^+ +1);

(2S,3R)-5-(3'-chloro-4'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 101), Mass (m/z): 496.12(M^+ +1);

(2S,3R)-5-(4'-butylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 102), Mass (m/z): 500.42(M^+ +1);

(2S,3R)-5-(2'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 103), Mass (m/z): 462.32(M^+ +1);

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 104), Mass (m/z): 466.31(M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 105), Mass (m/z): 462.38(M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 106), Mass (m/z): 513.35(M^+ +1);

(2S,3R)-5-[6-(3,4-difluorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 107), Mass (m/z): 481.32(M^+ +1);

(2S,3R)-5-[6-(4-chloro-3-fluorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 108), Mass (m/z): 497.30(M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[6-(4-fluorophenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 109), Mass (m/z): 463.35(M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[6-(3-fluoro-4-methylphenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 110), Mass (m/z): 477.34(M^+ +1);

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 111), Mass (m/z): 482.38(M^+ +1);

(2S,3R)-2-[2-(8-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 112),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 113), Mass (m/z): 484.39(M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 114), Mass (m/z): 542.36(M^+ +1);

(2S,3R)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 115), Mass (m/z): 472.12(M^+ +1);

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 116), Mass (m/z):476.23(M^+ +1);

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 117), Mass (m/z): 494.24(M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 118), Mass (m/z): 473.38(M^+ +1);

(2S,3R)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 119), Mass (m/z): 516.28(M^+ +1);

(2*R*,3*S*)-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. 120), Mass (m/z): 474.87(M^+ +1);

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 121), Mass (m/z): 510.23(M^+ +1);

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 122), Mass (m/z): 510.23(M^+ +1);

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 123), Mass (m/z): 512.31(M^+ +1);

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 124), Mass (m/z): 490.30(M^+ +1);

(2S,3R)-3-hydroxy-5-[4-(1-isobutyl-1H-pyrazol-4-yl)phenyl]-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 125), Mass (m/z): 504.33(M^+ +1);

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 126), Mass (m/z): 510.23(M^+ +1);

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 127), Mass (m/z): 492.26 (M^+ +1);

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 128), Mass (m/z): 510.30 (M^+ +1);

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 129), Mass (m/z): 504.38 (M^+ +1);

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 130), Mass (m/z): 547.29 (M^+ +1);

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 131), Mass (m/z): 549.30 (M^+ +1);

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 132), Mass (m/z): 547.29 (M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 133), Mass (m/z): 527.40 (M^+ +1);

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 134), Mass (m/z): 531.36 (M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 135), Mass (m/z): 488.34 (M^+ +1);

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 136), Mass (m/z): 494.33 (M^+ +1);

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 137), Mass (m/z): 494.33(M^+ +1);

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 138), Mass (m/z): 476.30 (M^+ +1);

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 139), Mass (m/z): 496.30 (M^+ +1);

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 140), Mass (m/z): 476.35 (M^+ +1);

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 141),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 142), Mass (m/z): 490.34(M^+ +1);

(2*S*,3*S*)-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. 143), Mass (m/z): 475.21(M^+ +1);

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 144), Mass (m/z): 512.32 (M^+ +1);

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 145), Mass (m/z): 514.37(M^+ +1);

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 146), Mass (m/z): 506.38 (M^+ +1);

(2S,3R)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 147), Mass (m/z): 532.38(M^+ +1);

(2S,3R)-5-[4-(6-chloropyridin-3-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 148), Mass (m/z): 479.36 (M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 149), Mass (m/z): 542.11(M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 150), Mass (m/z): 542.11(M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 151), Mass (m/z): 488.09 (M^+ +1);

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 152), Mass (m/z): 504.06 (M^+ +1);

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 153), Mass (m/z): 493.01(M^+ +1);

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 154), Mass (m/z): 523.02 (M^+ +1);

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 155), Mass (m/z): 511.04(M^+ +1);

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 156), Mass (m/z): 507.05 (M^+ +1);

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 157), Mass (m/z):507.05 (M^+ +1);

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 158), Mass (m/z): 504.09 (M^+ +1);

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 159), Mass (m/z): 508.03(M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 160), Mass (m/z): 505.11(M^+ +1);

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 161), Mass (m/z): 510.04(M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 162), Mass (m/z): 505.11(M^+ +1);

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 163), Mass (m/z): 526.95(M^+ +1);

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 164), Mass (m/z): 529.00 (M^+ +1);

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 165), Mass (m/z): 507.03(M^+ +1);

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 166), Mass (m/z): 476.01(M^+ +1);

(2S,3R)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 167), Mass (m/z): 489.05(M^+ +1);

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 168), Mass (m/z): 488.06 (M^+ +1);

(2S,3R)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 169), Mass (m/z): 472.03(M^+ +1);

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 170), Mass (m/z): 491.98 (M^+ +1);

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 171), Mass (m/z): 492.00(M^+ +1);

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 172), Mass (m/z): 509.98(M^+ +1);

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 173), Mass (m/z): 557.99 (M^+ +1);

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 174), Mass (m/z): 506.04(M^+ +1);

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 175), Mass (m/z): 526.91(M^+ +1);

(2S,3R)-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)-2-thienyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 176),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 177), Mass (m/z): 523.01(M^+ +1);

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 178),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 179), Mass (m/z): 489.07(M^+ +1);

(2S,3R)-5-[4-(2-chloropyridin-3-yl)phenyl]-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 180), Mass (m/z): 508.99(M^+ +1);

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 181), Mass (m/z): 493.19(M^+ +1);

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 182), Mass (m/z): 496.17(M^+ +1);

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 183), Mass (m/z): 498.15(M^+ +1);

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 184), Mass (m/z): 492.16 (M^+ +1);

(2S,3R)-3-hydroxy-5-[4-(2-methoxypyrimidin-5-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 185), Mass (m/z):476.13 (M^+ +1);

(2S,3R)-5-[2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 186), Mass (m/z):480.08 (M^+ +1);

(2S,3R)-5-[2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 187), Mass (m/z):480.15 (M^+ +1);

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl]-3-hydroxypentanoic acid (Cmpound No. 188), Mass (m/z):500.07 (M^+ +1);

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 189), Mass (m/z):500.13 (M^+ +1);

(2S,3R)-5-[2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 190), Mass (m/z):484.15 (M^+ +1);

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 191), Mass (m/z):502.16 (M^+ +1);

(2S,3R)-5-[2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 192), Mass (m/z):507.22(M^+ +23);

(2S,3R)-5-[2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 193),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(2-methoxypyrimidin-5-yl)phenyl]pentanoic acid (Compound No. 194), Mass (m/z):506.12 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(2-methoxypyrimidin-5-yl)phenyl]pentanoic acid (Compound No. 195), Mass (m/z):476.18 (M^+ +1);

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl) ethyl]pentanoic acid (Compound No. 196), Mass (m/z):465.26 (M^+ +1);

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 197), Mass (m/z):445.25 (M^+ +1);

(2S,3R)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-{2-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4H)-yl]ethyl}pentanoic acid (Compound No. 198), Mass (m/z):543.22 (M^+ +1);

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 199),Mass (m/z):474.25(M^+ +1);

(2S,3R)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)ethyl]pentanoic acid (Compound No. 200), Mass (m/z):454.24(M^+ +1);

(2S,3R)-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 201), Mass (m/z):495.27(M^+ +1);

(2S,3R)-2-[2-(2,4-dioxo-2H-1,3-benzoxazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 202), Mass (m/z):491.17(M^+ +1);

(2S,3R)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]pentanoic acid (Compound No. 203), Mass (m/z):470.12(M^+ +1);

(2S,3R)-5-(4-chloro-3-fluorophenyl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 204), Mass (m/z): 420.06 (M^+ +1);

(2R,3S)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 205), Mass (m/z): 476.07 (M^+ +1);

(2R,3S)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 206), Mass (m/z):462.03 (M^+ +1);

(2R,3S)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 207), Mass (m/z):480.03 (M^+ +1);

(2S,3S)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 208), Mass (m/z): 474.31 (M^+ +1);

(2S,3R)-3-hydroxy-5-[4-(5-methylpyridin-2-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 209), Mass (m/z): 459.21(M^+ +1);

(2S,3R)-5-[4-(6-fluoropyridin-3-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 210), Mass (m/z): 463.17(M^+ +1) ;

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 211), Mass (m/z): 530.33(M^+ +1) ;

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 212), Mass (m/z): 492.29(M^+ +1) ;

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 213), Mass (m/z): 490.34 (M^+ +1);

(2*S*,3*R*)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 214),

(2*S*,3*R*)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 215), Mass (m/z): 498.09 (M^+ +1);

(2*S*,3*R*)-5-(2',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 216), Mass (m/z): 466.06 (M^+ +1);

((2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 217), Mass (m/z): 448.07 (M^+ +1);

(2*S*,3*R*)-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 218), Mass (m/z): 478.22 (M^+ +1);

(2*S*,3*R*)-3-hydroxy-5-[4-(2-methoxypyrimidin-5-yl)phenyl]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 219), Mass (m/z): 462.23 (M^+ +1);

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 220), Mass (m/z): 461.23 (M^+ +1);

(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 221), Mass (m/z): 444.24 (M^+ +1);

(2*S*,3*R*)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 222), Mass (m/z): 514.14 (M^+ +1);

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl] pentanoic acid(Compound No. 223), Mass (m/z): 445.18 (M^+ +1);

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 224), Mass (m/z): 464.18 (M^+ +1);

(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 225) ,Mass (m/z): 466.20 (M^+ +1);

(2*S*,3*R*)-3-hydroxy-5-[4-(6-hydroxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid(Compound No. 226), Mass (m/z): 461.23 (M^+ +1);

(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-{2-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}pentanoic acid (Compound No. 227) ,Mass (m/z): 526.16 (M^+ +1);

(2*S*,3*R*)-2-[2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 228) ,Mass (m/z): 490.17 (M^+ +1)

(2*S*,3*R*)-3-(acetyloxy)-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid(Compound No. 229),Mass (m/z): 517.06(M^+ +1);

(2*S*,3*R*)-2-[2-(8-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid(Compound No. 230) Mass (m/z): 509.17 (M^+ +1);

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(2,4-dioxo-2*H*-1,3-benzoxazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 231), Mass (m/z): 493.93 (M^+ +1)

2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-(2-{[(2-hydroxyphenyl) carbonyl] amino}ethyl)pentanoic acid (Compound No. 232), Mass (m/z): 468.14 (M^+ +1)

Example: Assay for Matrix Metallo Proteinases (MMPs)

New chemical entities of the present invention and corresponding standards used in the present invention were prepared (stock 10 mM) in 100% DMSO and subsequent dilutions were made in 50% DMSO-50% TCNB (50 mM Tris, 10 mM $CaCl_2$, 150 mM NaCl, 0.05% Brij-35, pH 7.5). 1 µl of the compound and 88 µl of TCNB was added to wells of 96 well plate to achieve the desired final concentration of NCE (final DMSO concentration should not exceed 0.5%). 1 µl of activated, recombinant MMPs was added to each well (20-100 ng/100 µl reaction mixture) except the "negative well." (MMP-1, 9 &14 enzymes require prior activation. For this, supplied enzyme was incubated with

either APMA, final concentration 1 mM, for a time period of 1 hr at 37°C). Incubation was done at room temperature for 4-5 minutes. Reaction was initiated with 10 µl of 100 µM substrate (ES001: Aliquots were freshly diluted in TCNB; stock: 2 mM) and increase in florescence was monitored at excitation wavelength 320 nm followed by emission at 405 nm for 25-30 cycles. Increase in florescence (RFU) was calculated for positive, negative and NCE/standard wells. The percent inhibition compared to controls was calculated and IC_{50} values determined using Graph-prism software.

The present invention relates to compounds that act as dual MMP-9/12 inhibitors, which have desirable activity profiles and beneficial potency, selectivity and/or pharmacokinetic properties.

In particular, compounds disclosed herein exhibited activity in MMP9 assays from ≤ 0.02 nM to about 40 µM, or from ≤ 0.02 nM to about 200 nM, or from ≤ 0.02 nM to about 20 nM, or from ≤ 0.02 nM to about 1.0 nM, or from ≤ 0.02 nM to about 0.3 nM. Compounds disclosed herein exhibited activity in MMP12 assays from ≤ 0.02 nM to about 3.8 µM, or from ≤ 0.02 nM to about 200 nM, or from ≤ 0.02 nM to about 20 nM, or from ≤ 0.02 nM to about 1.0 nM, or from ≤ 0.02 nM to about 0.3 nM. Particular compounds tested (Nos. 2-28, 30, 32-43, 46, 50-51, 55-58, 60-61, 63, 65-69, 76, 79-80, 86-89, 93-96, 98, 106-107, 113-122, 126, 130-132, 134, 136-138, 143-144, 148-150, 155, 157, 159, 173-175, 177, 179, 181-182, 184-186, 190, 192-195, 198 and 210-211) exhibited activity in MMP1 assays from about 100 nM to about 10 µM, for example from about 100 nM to about 5 µM, or from about 100 nM to about 2 µM, or from about 100 nM to about 1 µM indicating that compounds of the present invention can be selective over MMP-1 by ≥ 100 fold.

Assay for *in vivo* LPS induced rat neutrophilia model

Male wistar rats were treated with vehicle / NCEs (new chemical entities) or standard drug and 2 hrs later challenged with Lipopolysaccharide (LPS) in Phosphate buffered saline (PBS), by oro-intra tracheal route (400µL of 50µg/ml). Negative control animals received PBS alone. Intratracheal instillation was done under Ketamine and Xylazine anaesthesia. Two hours post-LPS challenge, rats were euthanised and bronchoalveolar lavage (BAL) performed. The TLC, DLC was done to enumerate

neutrophil count in the BAL fluid and results were expressed as percent inhibition using the following formula

$$\% \text{ Inhibition} = \frac{\text{NeuLPS} - \text{NeuTEST}}{\text{NeuLPS} - \text{NeuPBS}} \times 100$$

Where,

NeuLPS = Neutrophil count in vehicle treated LPS challenged group

NeuTEST = Neutrophil count in group treated with a given dose of test compound

NeuPBS = Neutrophil in vehicle treated group challenged with PBS

Solubility Assessment

Equilibrium Solubility:

The pH-solubility profile of a compound is determined at 37°C in aqueous media with a pH in the range of 1-7.5. A sufficient number of pH conditions are evaluated to accurately define the pH-solubility profile. Standard buffer solutions described in the USP are considered appropriate for use in solubility studies.

The compound is weighed and transferred to the flasks. Media are added to each conical flask, the flask is sealed with stopper and paraffin film. The volume added is dependant upon the volume required for analysis of the content of the compound. The pH of the solution is measured after addition of the compound. The flask is observed intermittently. If the drug substance is completely dissolved, additional amount of the compound is added until saturation (undissolved residue is observed) and pH is measured. Flasks are removed from water bath after equilibrium is achieved. The saturated solution is filtered through 0.45 μm membrane filter and the samples are analyzed to estimate the content of the test compound.

Pharmacokinetic screening assays for Matrix Metallo Proteinase (MMP 9/12) inhibitors

Intrinsic clearance:

Intrinsic clearance (or metabolism stability) is assessed by estimating the rate of initial decay of parent compound in a suitable biological matrix like human liver microsomes.

The study reaction consists of NADPH regeneration system and liver microsomes of the various species of interest (human, rat dog, mouse), added into buffer at a concentration of 0.5 mg/mL. After a short preincubation the metabolic reaction is initiated by the addition of 5 µL of the substrate stock (100 µM) to yield a final concentration of 0.5 µM in the reaction. Periodic aliquots are drawn every three minutes until 30 minutes, quenched and the test compound concentration is estimated by LCMS. The rate of disappearance is estimated as the first order slope of the % parent remaining vs. time graph. The rate of decay is normalized to unit concentration of test compound and protein and extrapolated to 1g liver by using scaling factors (52.5 mg of CYP microsomal protein per gram of liver).

***Invitro* glucuronidation:**

A comparative assay in the form of intrinsic clearance (see above) with the addition of glucuronic acid and alamethacin to compare primarily the parent disappearance due to glucuronidation. Expressed as rate of clearance and normalized to per gram of liver.

Plasma protein binding:

Assessed by the equilibrium dialysis method where the unbound compound diffuses across a semi-permeable membrane and equilibrates with phosphate buffer (pH 7.4) is estimated, and is subtracted from the total drug in plasma to determine the percentage bound.

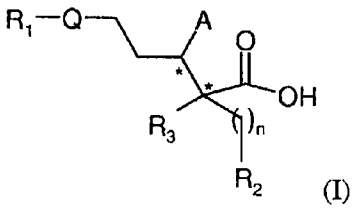
Equilibrium dialysis membranes are soaked overnight and the assembly is prepared. The test drug is spiked into plasma (100 and 1000 ng/mL) and incubated at 37°C and is transferred into the equilibrium apparatus with plasma added in one compartment and buffer in the other. The unit is rotated at constant rpm at 37°C for four hours to allow the unbound compound to dialyse and distribute with the buffer chamber. After four hours

the plasma and the buffer are removed from the respective compartments and the test compound concentrations are estimated. The percentage bound is estimated from the test compound concentrations.

Alternate methods include ultra filtration method where the compound spiked in plasma (100 and 1000 ng/mL) is filtered with Centricon filters (Millipore) having molecular weight cut off of (30000 DA) to prepare the retentate and ultra filtrate. The test compound is estimated in both and the percentage bound is calculated.

We Claim:

1. A compound of Formula I:



(I)

wherein:

* represents a stereogenic asymmetric center of defined configuration selected from (R, R), (S, S), (R, S) and (S,R);

n is an integer from 1 to 5;

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

R_2 is heterocyclyl, heteroaryl, 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;

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

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

wherein:

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

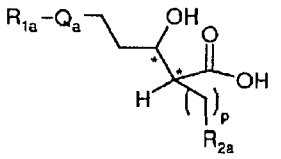
m is an integer 0-2; R_5 is hydrogen or R_4;

R_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, $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$;

Q is optionally substituted aryl or heteroaryl.

2. A compound of Formula Ia



(Ia)

wherein:

* denotes or represents a stereogenic or asymmetric center of defined configuration selected from (R, R), (S, S), (R, S) and (S,R);

p is an integer from 1 to 3;

R_{1a} is optionally substituted aryl or heteroaryl;

R_{2a} is 5-6 membered N-containing heterocyclyl linked through N atom, which is optionally fused to aryl, heteroaryl or spirofused to cycloalkyl, which can optionally be futher substituted with one or more oxo group, alkyl, cycloalkyl, halo, alkoxy, trifluoroalkyl or aryl

Q_a is optionally substituted 5 or 6 membered heteroaryl containing 1-4 heteroatom selected from O, N or S.

3. A compound which is selected from :

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 55),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[6-(4-methoxyphenyl)pyridin-3-yl]pentanoic acid (Compound No. 57),

(2*S*,3*R*)-5-[6-(4-chlorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 59),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 60),

(2*S*,3*R*)-5-[4-(4-chlorophenyl)-2-thienyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 61),

(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)-2-thienyl]pentanoic acid (Compound No. 62),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-{4-[4-(trifluoromethyl)phenyl]-2-thienyl}pentanoic acid (Compound No. 63),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-(3-fluoro-4-methoxyphenyl)-2-thienyl]-3-hydroxypentanoic acid (Compound No. 64),

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 106),

(2S,3R)-5-[6-(3,4-difluorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 107),

(2S,3R)-5-[6-(4-chloro-3-fluorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 108),

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[6-(4-fluorophenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 109),

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[6-(3-fluoro-4-methylphenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 110),

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 121),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 122),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 123),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 126),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 130),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 131),

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 132),

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 133),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 134),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 140),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 141),

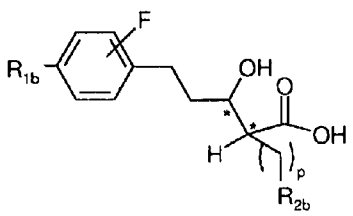
(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 142),

(2S,3R)-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)-2-thienyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 176),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 178),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 213),

4. A compound of Formula Ib



(Ib)

wherein:

* denotes or represents a stereogenic or asymmetric center of defined configuration selected from (R, R), (S, S), (R, S) and (S,R);

p is an integer from 1 to 3;

R_{1b} is optionally substituted pheny or heteroaryl, wherein optional substituents can be selected from with one or more alkyl, cycloalkyl, halo, alkoxy, trifluoroalkyl or aryl;

R_{2b} is 5-6 membered N-containing heterocyclyl linked through N atom, which is optionally fused to aryl, heteroaryl or spirofused to cycloalkyl, which can optionally be futher substituted with one or more oxo group, alkyl, halo, alkoxy, trifluoroalkyl or aryl.

5. A compound which is selected from :

(2*S*,3*R*)-5-(3,3'-difluoro-4'-methoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 47),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 50),

(2*S*,3*R*)-5-(4'-chloro-3-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 56),

(2*S*,3*R*)-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. 58),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 153),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 154),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 155),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 156),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 157),

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 163),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 164),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 165),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 175),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 177),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 186),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 187),

(2*S*,3*R*)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxypentanoic acid (Cmpound No. 188),

(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 189),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 190),

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 191),

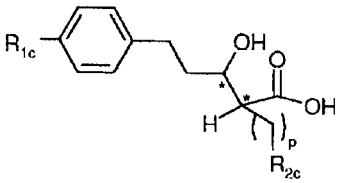
(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 192),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 193),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl) ethyl]pentanoic acid (Compound No. 196),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 197).

6. A compound of Formula Ic



(Ic)

wherein:

* denotes or represents a stereogenic or asymmetric center of defined configuration selected from (R, R), (S, S), (R, S) and (S,R);

p is an integer from 1 to 3;

R_{1c} is optionally substituted phenyl, pyridyl, pyrimidyl, thienyl or pyrazolyl; wherein optional substitutent can be selected from with one or more alkyl, halo, alkoxy, trifluoroalkyl or aryl;

R_{2c} is 5-6 membered N-containing heterocyclyl linked through N atom, which is optionally fused to aryl, heteroaryl or spirofused to cycloalkyl, which can optionally be futher substituted with one or more oxo group, alkyl, cycloalkyl, halo, alkoxy, trifluoro alkyl or aryl.

7. A compound which is selected:

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

(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-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 2),

(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. 3),

(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. 4),

(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. 5),

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

(2*S*,3*R*)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 7),

(2*S*,3*R*)-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. 8),

(2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 9),

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

(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 11),

(2*S*,3*R*)-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. 12),

(2*S*,3*R*)-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. 13),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 14),

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

(2*S*,3*R*)-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. 16),

(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. 17),

(2*S*,3*R*)-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. 18),

(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. 19),

(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. 20),

(2*S*,3*R*)-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. 21),

(2*S*,3*R*)-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. 22),

(2*S*,3*R*)-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. 23),

(2*S*,3*R*)-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. 24),

(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 25),

(2*S*,3*R*)-5-(4'-ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 26),

(2*S*,3*R*)-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. 27),

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 28),

(2*S*,3*R*)-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. 29),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 30),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyridin-3-ylphenyl)pentanoic acid (Compound No. 31),

(2*S*,3*R*)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 32),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 33),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 34),

(2*S*,3*R*)-3-hydroxy-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 35),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 36),

(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 37),

(2*S*,3*R*)-3-hydroxy-2-{2-[7-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 38),

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 39),

(2*S*,3*R*)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid(Compound No. 40),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 41),

(2*S*,3*R*)-3-hydroxy-2-{2-[5-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 42),

(2*S*,3*R*)-5-(4'-chloro-3'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 43),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-isobutyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 44),

(2*S*,3*R*)-5-biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 45),

(2*S*,3*R*)-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. 46),

(2*S*,3*R*)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 48),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1*H*-tetrazol-1-yl)phenyl]pentanoic acid (Compound No. 49),

(2*S*,3*R*)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 51),

(2*S*,3*R*)-3-hydroxy-5-[4-(1-isobutyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 52),

(2*S*,3*R*)-5-biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 53),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 54),

(2*S*,3*R*)-5-(4'-chloro-3-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 56),

(2*S*,3*R*)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 65),

(2*S*,3*R*)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 66),

(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 67),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 68),

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 69),

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

(2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 77),

(2*S*,3*R*)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 78),

(2*S*,3*R*)-2-[2-(5-chloro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 79),

(2*S*,3*R*)-2-[2-(4-fluoro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 80),

(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 81),

(2*S*,3*R*)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 90),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 91),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 92),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 93),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 94),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 95),

(2S,3R)-5-(2',4'-difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 97),

(2S,3R)-2-[2-(6-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 98),

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 99),

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-isopropylbiphenyl-4-yl)pentanoic acid (Compound No. 100),

(2S,3R)-5-(3'-chloro-4'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 101),

(2S,3R)-5-(4'-butylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 102),

(2S,3R)-5-(2'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 103),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 104),

(2S,3R)-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 105),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 111),

(2S,3R)-2-[2-(8-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 112),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 113),

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 114),

(2S,3R)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 115),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 116),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 117),

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 118),

(2S,3R)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 119),

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 124),

(2S,3R)-3-hydroxy-5-[4-(1-isobutyl-1H-pyrazol-4-yl)phenyl]-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 125),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]]pentanoic acid (Compound No. 127),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]]pentanoic acid (Compound No. 128),

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]]pentanoic acid (Compound No. 129),

(2S,3R)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 135),

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 136),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 137),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 138),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 139),

(2*S*,3*S*)-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. 143),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 144),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 145),

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 146),

(2S,3R)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 147),

(2S,3R)-5-[4-(6-chloropyridin-3-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 148),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 149),

(2S,3R)-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 150),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 151),

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 152),

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 158),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 159),

(2S,3R)-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 160),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 161),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 162),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 166),

(2S,3R)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 167),

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 168),

(2S,3R)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 169),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 170),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 171),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 172),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 173),

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 174),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 179),

(2S,3R)-5-[4-(2-chloropyridin-3-yl)phenyl]-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 180),

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 181),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 182),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 183),

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 184),

(2*S*,3*R*)-3-hydroxy-5-[4-(2-methoxypyrimidin-5-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 185),

(2*S*,3*R*)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(2-methoxypyrimidin-5-yl)phenyl]pentanoic acid (Compound No. 194),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(2-methoxypyrimidin-5-yl)phenyl]pentanoic acid (Compound No. 195),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-{2-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}pentanoic acid (Compound No. 198),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 199)

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 200),

(2*S*,3*R*)-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 201),

(2*S*,3*R*)-2-[2-(2,4-dioxo-2*H*-1,3-benzoxazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 202),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]pentanoic acid (Compound No. 203),

(2S,3R)-5-(4-chloro-3-fluorophenyl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 204),

(2R,3S)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 205),

(2*R*,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. 206),

(2*R*,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. 207),

(2*S*,3*S*)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 208),

(2*S*,3*R*)-3-hydroxy-5-[4-(5-methylpyridin-2-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 209),

(2*S*,3*R*)-5-[4-(6-fluoropyridin-3-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 210),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 211),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 212),

(2*S*,3*R*)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 214),

(2*S*,3*R*)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 215),

(2*S*,3*R*)-5-(2',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 216),

((2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 217),

(2*S*,3*R*)-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 218),

(2*S*,3*R*)-3-hydroxy-5-[4-(2-methoxypyrimidin-5-yl)phenyl]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 219),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 220),

(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 221),

(2*S*,3*R*)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 222),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 223),

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 224),

(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 225),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-hydroxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid(Compound No. 226),

(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-{2-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}pentanoic acid (Compound No. 227),

(2*S*,3*R*)-2-[2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 228),

(2*S*,3*R*)-2-[2-(8-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid(Compound No. 230),

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(2,4-dioxo-2*H*-1,3-benzoxazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 231).

8. A compound which is selected :

(2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid (Compound No. 82),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-phenylpentanoic acid (Compound No. 83),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4(trifluoromethyl)phenyl]pentanoic acid (Compound No. 84),

(2*S*,3*R*)-5-(4-*tert*-butylphenyl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.85),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[2-fluoro-5-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 70),

(2*S*,3*R*)-5-(4'-chloro-4-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 71),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[6-fluoro-4'-(trifluoromethyl)biphenyl-3-yl]-3-hydroxypentanoic acid (Compound No. 72),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-fluoro-3-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 73),

(2*S*,3*R*)-5-(4'-chloro-6-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 74),

(2*S*,3*R*)-5-(3',6-difluoro-4'-methoxybiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 75),

(2*S*,3*R*)-3-(acetyloxy)-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 229),

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-(2-{[(2-hydroxyphenyl)carbonyl]amino}ethyl)pentanoic acid (Compound No. 232).

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 and, together with pharmaceutically acceptable carriers, excipients or diluents.

10. The pharmaceutical composition of claim 9 further comprising one or more additional active ingredients selected from the group consisting of:

a. Anti-inflammatory agents, selected from (i) the nonsteroidal anti-inflammatory agents piroxicam, diclofenac, propionic acids, fenamates, pyrazolones, salicylates, PDE-4/p38 MAP Kinase/Cathepsin inhibitors, CCR-3 antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists, cell adhesion inhibitors, and adenosine 2a agonists (ii) leukotrienes LTC4/LTD4/LTE4/LTB4- Inhibitors, 5-lipoxygenase inhibitors and PAF- receptor antagonists, (iii) Cox-2 inhibitors; (iv) other MMP inhibitors; (v) interleukin-I inhibitors; (vi) the corticosteroids alclometasone, amcinonide, amelometasone, beclometasone, betamethasone, budesonide, ciclesonide, clobetasol, cloticasone, cyclomethasone, deflazacort, deprodone, dexbudesonide, diflorasone, difluprednate, fluticasone, flunisolide, halometasone, halopredone, hydrocortisone, hydrocortisone, methylprednisolone, mometasone, prednicarbate, prednisolone, rimexolone, tixocortol, triamcinolone, ulobetasol, rofleponide, GW 215864, KSR 592, ST-126, dexamethasone and pharmaceutically acceptable salts, solvates thereof;

b) Beta-agonists, selected from the β2-agonists albuterol, salbutamol, biltolterol, pirbuterol, levosalbutamol, tulobuterol, terbutaline, bambuterol, metaproterenol, fenoterol, salmeterol, carmoterol, arformoterol, formoterol, and their pharmaceutically acceptable salts or solvates thereof;

c) antihypertensive agents selected from (i) the ACE inhibitors, enalapril, lisinopril, valsartan, telmisartan and quinapril, (ii) the angiotensin II

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receptor antagonists and agonists losartan, candesartan, irbesartan, valsartan, and eprosartan, (iii) β-blockers, and (iv) calcium channel blockers;

d) immunosuppressive agents selected from cyclosporine, azathioprine and methotrexate, anti-inflammatory corticosteroids; and

e) the antiinfective agents antibiotics, and antivirals.

11. A method for treatment or prophylaxis of an animal or a human suffering from an inflammatory disease or autoimmune disorder which comprises administering to the animal or human an effective amount of a compound according to claim 1-8.

12. A method for treatment or prophylaxis of an animal or a human suffering from an inflammatory disease or autoimmune disorder which comprises administering to the animal or human an effective amount of pharmaceutical composition according to claim 9.

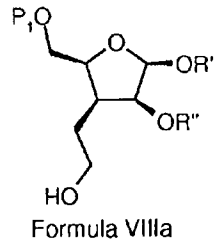
13. A method for treatment or prophylaxis of an animal or a human suffering from an inflammatory disease or autoimmune disorder which comprises administering to the animal or human an effective amount of pharmaceutical composition according to claim 10.

14. A chiral auxiliary which is (4S)-4-benzyl-1,3-thiazolidin-2-one.

15. Use of a chiral auxiliary of claim 14 in chemical synthetic transformation reactions selected from asymmetric aldol condensation, stereoselective alkylation, stereoselective Diels-Alder reaction, stereoselective Michael reactions, stereoselective differentiation reactions of enantiotopic groups in molecules bearing prochiral centers

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

a. reacting a compound of Formula VIIIa



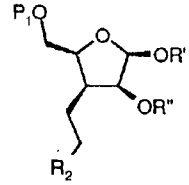
Formula VIIIa

with a compound of Formula IX

R_2-H

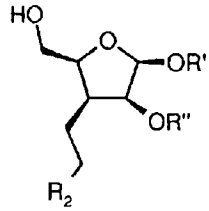
Formula IX

to give a compound of Formula X;



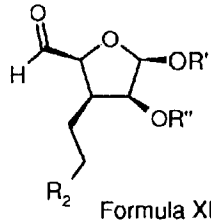
Formula X

b. deprotecting the compound of Formula X to give a compound of Formula XI;



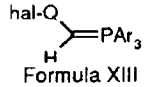
Formula XI

c. oxidizing the compound of Formula XI to give a compound of Formula XII;



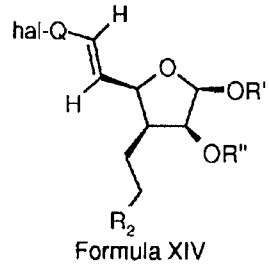
Formula XII

d. reacting the compound of Formula XII with a compound of Formula XIII



Formula XIII

to give a compound of Formula XIV;



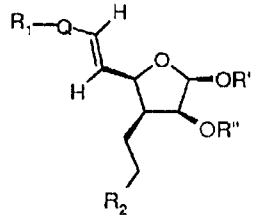
Formula XIV

e. reacting the compound of Formula XIV with a compound of Formula XV

R_1-B(OH)$_2$

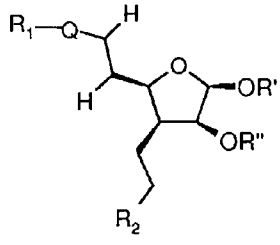
Formula XV

to give a compound of Formula XVI;



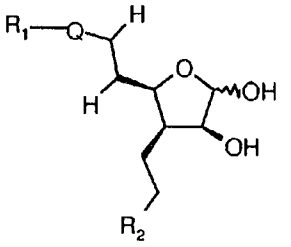
Formula XVI

f. hydrogenating a compound of Formula XVI to give a compound of Formula XVII



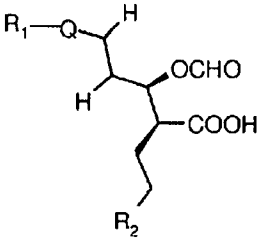
Formula XVII

g. deprotecting the compound of Formula XVII to give a compound of Formula XVIII;



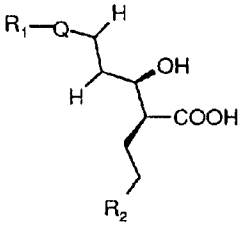
Formula XVIII

h. converting the compound of Formula XVIII to a compound of Formula XIX; and



Formula XIX

i. deformylating the compound of Formula XIX to give the compound of Formula XX.



Formula XX

wherein:

P_1 is a silyl protecting group;

R' and R" together form an acetal protecting group;

R_2 is an N-containing heterocyclyl or heteroaryl;

hal is Cl, Br or I;

Ar is phenyl;

Q is optionally substituted aryl or heteroaryl; and

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

17. The process according to claim 16, wherein compounds of Formula XX are selected from:

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

(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-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 2),

(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. 3),

(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. 4),

(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. 5),

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

(2*S*,3*R*)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 7),

(2*S*,3*R*)-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. 8),

(2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 9),

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

(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 11),

(2*S*,3*R*)-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. 12),

(2*S*,3*R*)-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. 13),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 14),

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

(2*S*,3*R*)-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. 16),

(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. 17),

(2*S*,3*R*)-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. 18),

(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. 19),

(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. 20),

(2*S*,3*R*)-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. 21),

(2*S*,3*R*)-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. 22),

(2*S*,3*R*)-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. 23),

(2*S*,3*R*)-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. 24),

(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 25),

(2*S*,3*R*)-5-(4'-ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 26),

(2*S*,3*R*)-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. 27),

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 28),

(2*S*,3*R*)-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. 29),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 30),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyridin-3-ylphenyl)pentanoic acid (Compound No. 31),

(2*S*,3*R*)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 32),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 33),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 34),

(2*S*,3*R*)-3-hydroxy-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 35),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 36),

(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 37),

(2*S*,3*R*)-3-hydroxy-2-{2-[7-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 38),

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 39),

(2*S*,3*R*)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid(Compound No. 40),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 41),

(2*S*,3*R*)-3-hydroxy-2-{2-[5-(6-methoxypyridin-3-yl)-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 42),

(2*S*,3*R*)-5-(4'-chloro-3'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 43),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1-isobutyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 44),

(2*S*,3*R*)-5-biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 45),

(2*S*,3*R*)-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. 46),

(2*S*,3*R*)-5-(3,3'-difluoro-4'-methoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 47),

(2*S*,3*R*)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 48),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(1*H*-tetrazol-1-yl)phenyl]pentanoic acid (Compound No. 49),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 50),

(2*S*,3*R*)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 51),

(2*S*,3*R*)-3-hydroxy-5-[4-(1-isobutyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 52),

(2*S*,3*R*)-5-biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 53),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 54),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 55),

(2*S*,3*R*)-5-(4'-chloro-3-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 56),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[6-(4-methoxyphenyl)pyridin-3-yl]pentanoic acid (Compound No. 57),

(2*S*,3*R*)-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. 58),

(2*S*,3*R*)-5-[6-(4-chlorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 59),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 60),

(2*S*,3*R*)-5-[4-(4-chlorophenyl)-2-thienyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 61),

(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)-2-thienyl]pentanoic acid (Compound No. 62),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-{4-[4-(trifluoromethyl)phenyl]-2-thienyl}pentanoic acid (Compound No. 63),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-(3-fluoro-4-methoxyphenyl)-2-thienyl]-3-hydroxypentanoic acid (Compound No. 64),

(2*S*,3*R*)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 65),

(2*S*,3*R*)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 66),

(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 67),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 68),

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 69),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[2-fluoro-5-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 70),

(2*S*,3*R*)-5-(4'-chloro-4-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 71),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[6-fluoro-4'-(trifluoromethyl)biphenyl-3-yl]-3-hydroxypentanoic acid (Compound No. 72),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4-fluoro-3-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 73),

(2*S*,3*R*)-5-(4'-chloro-6-fluorobiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 74),

(2*S*,3*R*)-5-(3',6-difluoro-4'-methoxybiphenyl-3-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 75),

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

(2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 77),

(2*S*,3*R*)-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 78),

(2*S*,3*R*)-2-[2-(5-chloro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 79),

(2*S*,3*R*)-2-[2-(4-fluoro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 80),

(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 81),

(2*S*,3*R*)-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. 86),

(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. 87),

(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.88),

(2*S*,3*R*)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 90),

(2*S*,3*R*)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 91),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 92),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 93),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 94),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 95),

(2S,3R)-5-(2',4'-difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 97),

(2S,3R)-2-[2-(6-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 98),

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 99),

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-isopropylbiphenyl-4-yl)pentanoic acid (Compound No. 100),

(2S,3R)-5-(3'-chloro-4'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 101),

(2S,3R)-5-(4'-butylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 102),

(2S,3R)-5-(2'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 103),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 104),

(2S,3R)-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 105),

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 106),

(2S,3R)-5-[6-(3,4-difluorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 107),

(2S,3R)-5-[6-(4-chloro-3-fluorophenyl)pyridin-3-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 108),

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[6-(4-fluorophenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 109),

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[6-(3-fluoro-4-methylphenyl)pyridin-3-yl]-3-hydroxypentanoic acid (Compound No. 110),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 111),

(2S,3R)-2-[2-(8-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 112),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]pentanoic acid (Compound No. 113),

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 114),

(2S,3R)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 115),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 116),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 117),

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 118),

(2S,3R)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 119),

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 121),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 122),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 123),

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 124),

(2S,3R)-3-hydroxy-5-[4-(1-isobutyl-1H-pyrazol-4-yl)phenyl]-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 125),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)pentanoic acid (Compound No. 126),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 127),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 128),

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 129),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 130),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 131),

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 132),

(2S,3R)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 133),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-{6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}pentanoic acid (Compound No. 134),

(2S,3R)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 135),

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 136),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 137),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 138),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 139),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 140),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 141),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 142),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 144),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 145),

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 146),

(2S,3R)-5-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-3-hydroxy-2-[2-(8-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 147),

(2S,3R)-5-[4-(6-chloropyridin-3-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 148),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 149),

(2S,3R)-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 150),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 151),

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 152),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 153),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 154),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 155),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 156),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 157),

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 158),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 159),

(2S,3R)-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 160),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 161),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 162),

(2S,3R)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 163),

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 164),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 165),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 166),

(2S,3R)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 167),

(2S,3R)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 168),

(2S,3R)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 169),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 170),

(2S,3R)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 171),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 172),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 173),

(2S,3R)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 174),

(2S,3R)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 175),

(2S,3R)-3-hydroxy-5-[4-(1-methyl-1H-pyrazol-4-yl)-2-thienyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 176),

(2S,3R)-5-[2-fluoro-4-(6-methoxypyridin-3-yl)phenyl]-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 177),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 178),

(2S,3R)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 179),

(2S,3R)-5-[4-(2-chloropyridin-3-yl)phenyl]-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 180),

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 181),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 182),

(2S,3R)-5-(3',4'-difluorobiphenyl-4-yl)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 183),

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 184),

(2*S*,3*R*)-3-hydroxy-5-[4-(2-methoxypyrimidin-5-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 185),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(6-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 186),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 187),

(2*S*,3*R*)-2-[2-(5-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxypentanoic acid (Cmpound No. 188),

(2*S*,3*R*)-2-[2-(7-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 189),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 190),

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxypentanoic acid (Compound No. 191),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 192),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 193),

(2*S*,3*R*)-3-hydroxy-2-[2-(6-methoxy-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4-(2-methoxypyrimidin-5-yl)phenyl]pentanoic acid (Compound No. 194),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(2-methoxypyrimidin-5-yl)phenyl]pentanoic acid (Compound No. 195),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl) ethyl]pentanoic acid (Compound No. 196),

(2*S*,3*R*)-5-[2-fluoro-4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 197),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-{2-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}pentanoic acid (Compound No. 198),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 199),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 200),

(2*S*,3*R*)-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 201),

(2*S*,3*R*)-2-[2-(2,4-dioxo-2*H*-1,3-benzoxazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 202),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]pentanoic acid (Compound No. 203),

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 211),

(2S,3R)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 212),

(2S,3R)-3-hydroxy-5-(6'-methoxy-2,3'-bipyridin-5-yl)-2-[2-(8-methyl-4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 213),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-hydroxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid(Compound No. 226),

(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-{2-[4-oxo-7-(trifluoromethyl)-1,2,3-benzotriazin-3(4*H*)-yl]ethyl}pentanoic acid (Compound No. 227),

(2*S*,3*R*)-2-[2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 228),

(2*S*,3*R*)-3-(acetyloxy)-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 229),

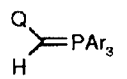
(2*S*,3*R*)-2-[2-(8-chloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid(Compound No. 230),

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(2,4-dioxo-2*H*-1,3-benzoxazin-3(4*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 231), and

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-(2-{[(2-hydroxyphenyl) carbonyl]amino}ethyl) pentanoic acid (Compound No. 232) .

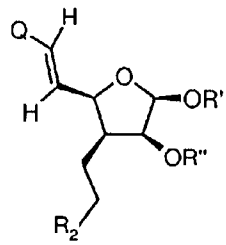
18. A process for preparing a compound of Formula XXVI comprising:

a. reacting a compound of Formula XII with a compound of Formula XXI



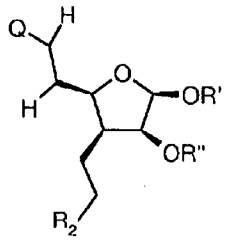
Formula XXI

to give a compound of Formula XXII;



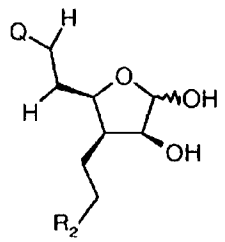
Formula XXII

b. hydrogenating the compound of Formula XXII to give a compound of Formula XXIII;



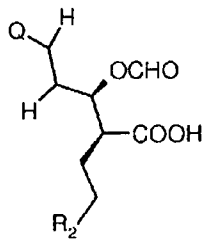
Formula XXIII

c. deprotecting the compound of Formula XXIII to give a compound of Formula XXIV;



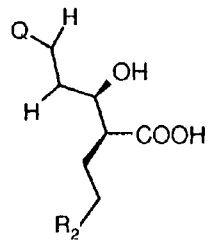
Formula XXIV

d. converting the compound of Formula XXIV to a compound of Formula XXV; and



Formula XXV

e. deformylating the compound of Formula XXV to give the compound of Formula XXVI,.



Formula XXVI

wherein

R' and R" together form an acetal protecting group;

R_2 is an N-containing heterocyclyl or heteroaryl;

Ar is phenyl; and

Q is optionally substituted aryl or heteroaryl.

19. The process according to claim 18, wherein compounds of Formula XXVI are selected from:

(2S,3R)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-phenylpentanoic acid (Compound No. 82),

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-phenylpentanoic acid (Compound No. 83),

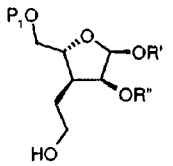
(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4(trifluoromethyl)phenyl]pentanoic acid (Compound No. 84),

(2*S*,3*R*)-5-(4-*tert*-butylphenyl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.85), and

(2S,3R)-5-(4-chloro-3-fluorophenyl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 204).

20. A process for preparing a compound of Formula XXXV comprising:

a. reacting a compound of Formula VIIIb



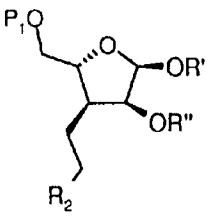
Formula VIIIb

with a compound of Formula IX

R_2-H

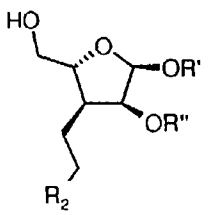
Formula IX

to give a compound of Formula XXVII;



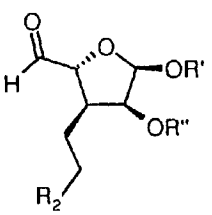
Formula XXVII

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



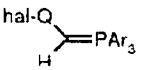
Formula XXVIII

c. oxidizing the compound of Formula XXVIII to give a compound of Formula XXIX;



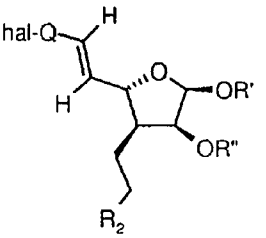
Formula XXIX

d. reacting the compound of Formula XXIX with a compound of Formula XIII



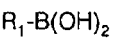
Formula XIII

to give a compound of Formula XXX;



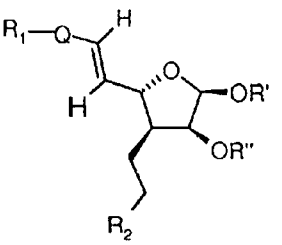
Formula XXX

e. reacting the compound of Formula XXX with a compound of Formula XV



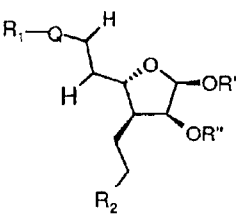
Formula XV

to give a compound of Formula XXXI;



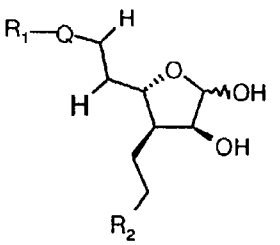
Formula XXXI

f. hydrogenating the compound of Formula XXXI to give a compound of Formula XXXII;



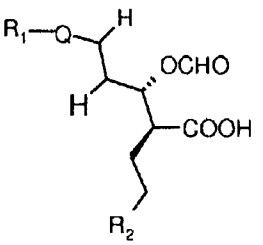
Formula XXXII

g. deprotecting the compound of Formula XXXII to give a compound of Formula XXXIII;



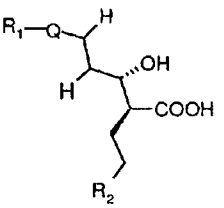
Formula XXXIII

h. converting the compound of Formula XXXIII to a compound of Formula XXXIV; and



Formula XXXIV

i. deformylating the compound of Formula XXXIV to give a compound of Formula XXXV,



Formula XXXV

wherein

P_1 is a silyl protecting group;

R' and R" together form an acetal protecting group;

R_2 is N-containing heterocyclyl or heteroaryl;

hal is Cl, Br or I;

PATENTE DE INVENCION

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TOMO: 213

Ar is phenyl;

Q is optionally substituted aryl or heteroaryl; and

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

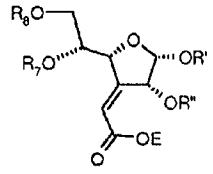
21. The process according to claim 20, wherein compounds of Formula XXXV are selected from:

(2*S*,3*S*)-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. 143),

(2*S*,3*S*)-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 208).

22. A process for preparing a compound of Formula LIII comprising:

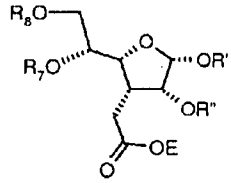
a. converting a compound of Formula XLI to a compound of Formula XLII



Formula XLII

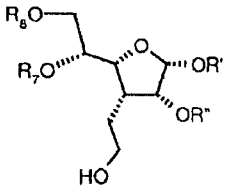
by reaction with a Wittig reagent;

b. hydrogenating the compound of Formula XLII to give a compound of Formula XLIII;



Formula XLIII

c. reducing the compound of Formula XLIII to give a compound of Formula XLIV;



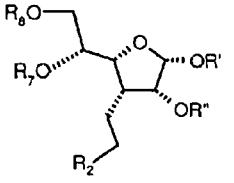
Formula XLIV

d. reacting the compound of Formula XLIV with a compound of Formula IX



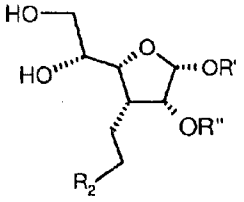
Formula IX

to give a compound of Formula XLV;



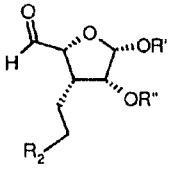
Formula XLV

e. deprotecting the compound of Formula XLV to give a compound of Formula XLVI;



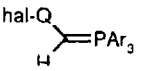
Formula XLVI

f. oxidizing the compound of Formula XLVI to give a compound of Formula XLVII;



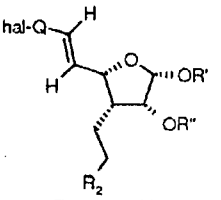
Formula XLVII

g. reacting the compound of Formula XLVII with a compound of Formula XIII



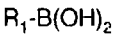
Formula XIII

to give a compound of Formula XLVIII;



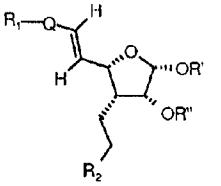
Formula XLVIII

h. reacting the compound of Formula XLVIII with a compound of Formula XV



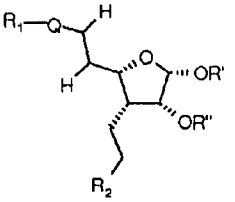
Formula XV

to give a compound of Formula XLIX;



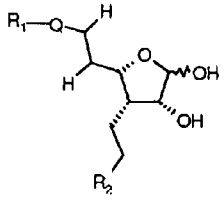
Formula XLIX

i. hydrogenating the compound of Formula XLIX to give a compound of Formula L;



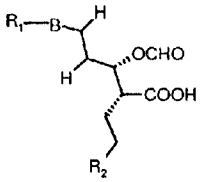
Formula L

j. deprotecting the compound of Formula L to give a compound of Formula LI;



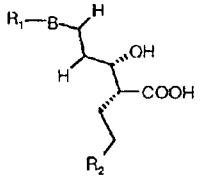
Formula LI

k. converting the compound of Formula LI to a compound of Formula LII; and



Formula LII

l. deformylating the compound of Formula LII to give the compound of Formula LIII,



Formula LIII

wherein

R_7 and R_8 together form acetal protecting group;

R' and R" together form an acetal protecting group;

E is an alkyl group;

R_2 is an N-containing heterocyclyl or heteroaryl;

hal is Cl, Br or I;

Ar is phenyl;

Q is optionally substituted aryl or heteroaryl; and

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

23. The process according to claim 22, wherein compounds of Formula LIII are selected from:

(2*R*,3*S*)-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. 120),

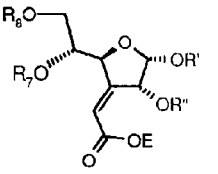
(2R,3S)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 205),

(2*R*,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. 206), and

(2*R*,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. 207).

24. A process for preparing a compound of Formula LXVI comprising:

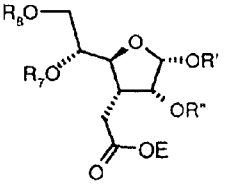
a. converting a compound of Formula XXXVII to a compound of Formula LIV



Formula LIV

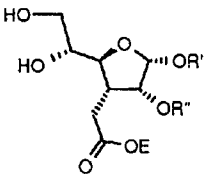
by reaction with a Wittig reagent;

b. hydrogenating the compound of Formula LIV to give a compound of Formula LV;



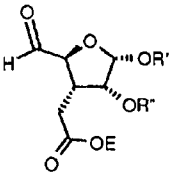
Formula LV

c. deprotecting the compound of Formula LV to give a compound of Formula LVI;



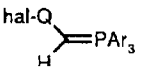
Formula LVI

d. oxidizing the compound of Formula LVI to give a compound of Formula LVII;



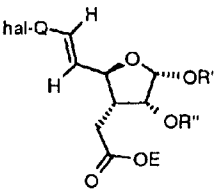
Formula LVII

e. reacting the compound of Formula LVII with a compound of Formula XIII



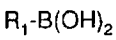
Formula XIII

to give a compound of Formula LVIII;



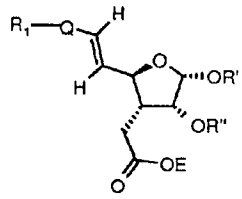
Formula LVIII

f. reacting the compound of Formula LVIII with a compound of Formula XV



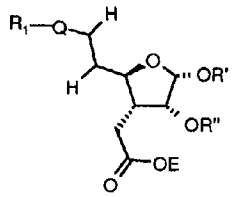
Formula XV

to give a compound of Formula LIX;



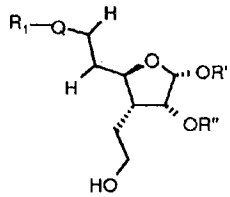
Formula LIX

g. hydrogenating the compound of Formula LIX to give a compound of Formula LX;



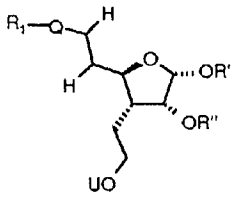
Formula LX

h. deprotecting the compound of Formula LX to give a compound of Formula LXI;



Formula LXI

i. activating the compound of Formula LXI to a compound of Formula LXII;



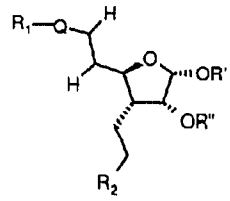
Formula LXII

j. reacting the compound of Formula LXII with a compound of Formula IXa.



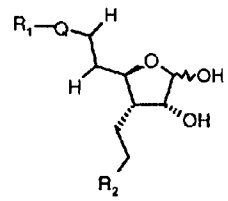
Formula IXa

to give a compound of Formula LXIII;



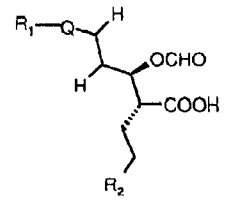
Formula LXIII

k. deprotecting the compound of Formula LXIII to give a compound of Formula LXIV;



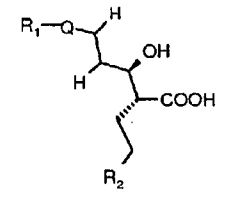
Formula LXIV

l. converting the compound of Formula LXIV to a compound of Formula LXV; and



Formula LXV

m. deformylating the compound of Formula LXV to give the compound of Formula LXVI,



Formula LXVI

wherein

R_7 and R_8 together form a acetal protecting group;

R' and R" together form an acetal protecting group;

R_2 is an N-containing heterocyclyl or heteroaryl;

U is an O-activating group;

E is an alkyl group;

hal is Cl, Br or I;

Ar is phenyl;

M is a metal;

Q is an optionally substituted aryl or heteroaryl; and

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

25. The process according to claim 24, wherein compounds of Formula LXVI are selected from:

(2R,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.89),and

(2*R*,3*R*)-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. 96).

26. A process for preparing a compound of Formula XX comprising:

a. reacting a compound of Formula LXVII

R_1-hal

Formula LXVII

with a compound of Formula LXVIII

$(OH)_2B$-Q-CHO

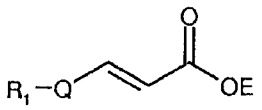
Formula LXVIII

to give a compound of Formula LXIX;

R_1—Q—CHO

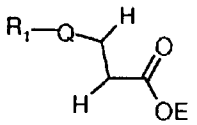
Formula LXIX

b. converting the compound of Formula LXIX to a compound of Formula LXX;



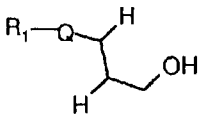
Formula LXX

c. hydrogenating the compound of Formula LXX to give a compound of Formula LXXI;



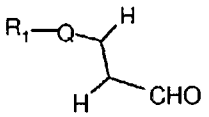
Formula LXXI

d. reducing the compound of Formula LXXI to give a compound of Formula LXXII;



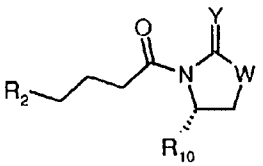
Formula LXXII

e. oxidizing the compound of Formula LXXII to give a compound of Formula LXXIII;



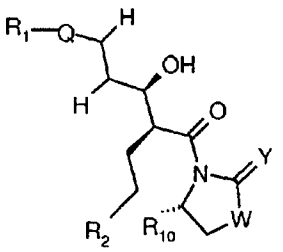
Formula LXXIII

f. reacting the compound of Formula LXXIII with a compound of Formula LXXIV



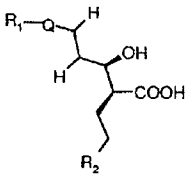
Formula LXXIV

to give a compound of Formula LXXV; and



Formula LXXV

g. hydrolyzing the compound of Formula LXXV to give a compound of Formula XX,



Formula XX

wherein

R_2 is an N-containing heterocyclyl or heteroaryl,

E is an alkyl group;

hal is Cl, Br or I;

Q is an optionally substituted aryl or heteroaryl;

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

Y and W are independently oxygen or sulphur; and

R_{10} is alkyl, aryl or aralkyl.

27. The process according to claim 26 wherein compounds of Formula XX are selected from:

(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. 86),

(2*S*,3*R*)-3-hydroxy-5-[4-(5-methylpyridin-2-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 209),

(2*S*,3*R*)-5-[4-(6-fluoropyridin-3-yl)phenyl]-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 210),

(2*S*,3*R*)-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 214),

(2*S*,3*R*)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 215),

(2*S*,3*R*)-5-(2',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 216),

((2*S*,3*R*)-5-(4'-fluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 217),

(2*S*,3*R*)-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 218),

(2*S*,3*R*)-3-hydroxy-5-[4-(2-methoxypyrimidin-5-yl)phenyl]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 219),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 220),

(2*S*,3*R*)-3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 221),

(2*S*,3*R*)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 222),

(2*S*,3*R*)-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid(Compound No. 223),

(2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 224), and

(2*S*,3*R*)-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxy-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl]pentanoic acid (Compound No. 225).

TRADUCCIÓN PÚBLICA: ----------

INHIBIDORES DE LA METALOPROTEINASA MATRIZ. ----------

Campo del Invento. ----------

El presente invento se relaciona con ciertos ácidos carboxílicos β-hidroxi- y amino-sustituidos como los inhibidores de la metaloproteasa matriz, especialmente los ácidos carboxílicos-β-hidroxi diastereoméricamente puros y a los procesos para sus síntesis. ----------

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Este invento también se relaciona con composiciones farmacológicas que contienen los compuestos del presente invento, y con los métodos para tratar el asma, artritis reumatoidea, COPD, rinitis, osteoartritis, artritis soriásica, psoriasis, fibrosis pulmonar, desórdenes en la cura de heridas, inflamación pulmonar, síndrome de perturbación respiratoria aguda, periodontitis, esclerosis múltiple, gingivitis, ateroesclerosis, proliferación neoíntima, que lleva a la restenosis y a la insuficiencia cardíaca isquémica, ataque apopléjico, enfermedades renales, metástasis tumoral, y demás desórdenes inflamatorios caracterizados por la hiper-expresión y la hiper-activación de una metaloproteinasa matriz utilizando los compuestos. --

Antecedentes del Invento. ----------

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Las metaloproteinasas (MMPs) son una superfamilia que surge naturalmente de las proteinasas (enzimas) que se encuentran en la mayoría de los mamíferos. La superfamilia se compone

de por lo menos 26 miembros de las enzimas que contienen zinc producidas por muchos tipos de células y compartiendo características estructurales y funcionales. En base a las consideraciones estructurales y funcionales las proteinasas han sido clasificadas en diferentes familias y subfamilias (Vartak et al., (2007), *J. Drug Targeting*, 15, 1-20; y Hopper, (1994), *FEBS*, 354, 1-6), como ser las colagenasas (MMP-1, -8 y -13), gelatinasas (MMP-2, y ——9), metaloelastasas (MMP-12), las MT-MMPs (MMP-14, —15, -16, -17, - 24 y 25), matrilisinas (MMP-7 y -26), estromelisinas (MMP-3, -10 y -11) y *sheddases* como por ejemplo las enzimas que convierten el TNF (TACE, y ACE). ----------

Se cree que las metaloproteinasas son importantes en los procesos de enfermedad fisiológica que involucran la remodelación tal como en el desarrollo embrionario, formación ósea y remodelación uterina durante la menstruación. Una función biológica principal de las MMPs es catalizar la desintegración de los tejidos conectivos o de la matriz extra celular mediante su capacidad para hidrolizar diversos componentes de tejido o matriz. Además de su papel en la degradación del tejido conectivo, las MMPs están involucradas en la activación de las (pro) formas de cimógeno de otras MMPs induciendo de ahí la activación MMP. También están involucradas en la biosíntesis del TNF-alfa que se encuentra implicada en muchos estados patológicos. --

La MMP-12, también conocida como macrófago elastasa o metaloelastasa, se expresa en macrófagos activados y ha

sido demostrado que se secreta de macrófagos alveolares de fumadores como asimismo en las células esponjosas en lesiones ateroescleróticas. Los estudios de la MMP-12 en ratón desmayado han demostrado el desarrollo de enfisema significativo, respaldando de ese modo su papel en el COPD. La MMP-9 (gelatinasa B, 92 kDa tipo colagenasa IV) es un miembro de la familia de la MMP que se libera como una proenzima y posteriormente se activa a través de una cascada proteasa *in vivo*. ----------

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La concentración de MMP-9 aumenta en enfermedades como el asma, la fibrosis pulmonar intersticia (IPF), el síndrome de perturbación respiratoria en adultos (ARDS), y en la enfermedad pulmonar obstructiva crónica (COPD). A causa de su capacidad proteolítica, la MMP-9 ha sido involucrada en la remodelación del tejido de las vías aéreas y de los pulmones en las enfermedades inflamatorias crónicas como por ejemplo asma grave y COPD. También es probable que la MMP-9 resulte fisiológicamente importante debido a su capacidad para regular la digestión de los componentes de la matriz extracelular como asimismo la actividad de otras proteasas y citoquinas. La MMP-9 se excreta en neutrófilos, macrófagos, osteoclastos, que resultan fácilmente inducidos por las citoquinas y los factores de crecimiento, y juega un rol en diversos procesos fisiológicos y patológicos. ---

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Se ha vinculado la hiper-expresión o la hiper-activación de una MMP, o de un desequilibrio entre una MMP y un inhibidor de tejido natural (es decir, endógeno) de una matriz

metaloproteinasa (TIMP) con una patogénesis de enfermedades caracterizadas por la desintegración del tejido conectivo o de la matriz extracelular. ----------

La inhibición de la actividad de una o más MMPs podrá resultar beneficiosa en el tratamiento de diversos desórdenes inflamatorios, enfermedades de autoinmunidad y enfermedades alérgicas tales como, inflamación de articulaciones, inflamación del tracto GI, inflamación de la piel, remodelación de colágeno, desórdenes en la curación de heridas, etc. ----------

El diseño y la aplicación terapéutica de los inhibidores de la MMP ha revelado que el requisito de una molécula para resultar en inhibidor efectivo de la clase de enzimas MMP es un grupo funcional (por ej. Ácido carboxílico, ácido hidroxámico o sulfidrilo) capaz de quelar el lugar activo del ion Zn^{2+} (Whittaker *et al.*, *Chem. Rev.*, (1999), 99; 2735-76). ----------

La WO 2004/110974 revela compuestos y sus derivados fisiológicamente funcionales descriptos como inhibidores de las enzimas metaloproteinasa matriz. La WO 2004/113279 revela presuntos inhibidores de la metaloproteinasa matriz. La WO 2005/026120 revela compuestos también descriptos como inhibidores de la metaloproteinasa matriz. La Patente Norteamericana Nro. 6,350,885 revela compuestos heteroaromáticos tricíclicos y sus derivados que se cree

que inhiben las metaloproteinasa matriz. La WO 98/09940 revela ácidos butíricos bifenilos y sus derivados descriptos como inhibidores de las metaloproteinasas matriz. La *J. Med. Chem.*, (1968), vol. 11(6), 1139-1144 revela la síntesis y la actividad anti-inflamatoria del 4-(p-bifenilil)-3-ácido hidroxibutírico y de los compuestos relacionados. La WO 96/15096 revela ácidos 4-biarilbutirico ó 5-biarilpentanoico sustituido y derivados como presuntos inhibidores de la metaloproteinasa matriz. La WO 2006/090235 describe los derivados del ácido 5-fenil-pentanoico descriptos como inhibidores de la metaloproteinasa matriz para el tratamiento del asma y otras enfermedades. ----------

Se ha llevado a cabo la investigación con respecto a la identificación de los inhibidores que son selectivos, *por ej.*, para algunos de los subtipos de la MMP. Un inhibidor de la MMP de selectividad mejorada evitaría efectos colaterales potenciales asociados con la inhibición de las MMPs que no están involucradas en la patogénesis de la enfermedad a tratar. ----------
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Asimismo, el uso de inhibidores más selectivos de la MMP requeriría la administración de una cantidad menor del inhibidor que de otro modo se requeriría para el tratamiento de la enfermedad, después de la administración, dividido *in vivo* entre MMPs múltiples. Más aún, la administración de una cantidad menor del compuesto mejoraría el margen de seguridad entre la dosis del inhibidor requerido para la actividad terapéutica y la

dosis del inhibidor en la cual se observa toxicidad. ------

Existen muchas drogas como moléculas tridimensionales asimétricas, es decir, quiral y por lo tanto tendrán algunos estereoisómeros dependiendo de la cantidad de centros quirales presentes. La importancia de evaluar nuevas entidades químicas que tienen centros quirales como isómeros simples es para entender su efecto sobre los aspectos farmacológicos y toxicológicos. A menudo se encuentran diferencias farmacodinámicas, farmacocinéticas y/o toxicológicas entre enantiómeros / diastereómeros. Aunque los mediadores fisiológicos naturales son aquirales, en base al ambiente apuntado, sus receptores/enzimas podrán demostrar una preferencia solamente para un enantiómero óptimamente puro de agonistas, antagonistas o inhibidores. Desde un punto de vista farmacocinético, la quiralidad podrá tener influencia sobre la absorción, distribución, metabolismo y eliminación de la droga. Los isómeros simples puros podrán también ofrecer ventajas en términos de estos parámetros farmacocinéticos permitiendo de esa forma mejor desarrollo de esas moléculas como drogas candidatas. También se sabe que la quiralidad tiene un efecto significativo de las propiedades físico-químicas y cristalinidad de una molécula quiral que a su vez tendrá efectos profundos sobre la farmacocinética y desarrollo de la molécula. Además de los mencionados precedentemente, los principios reglamentarios lo guían a uno a desarrollar preferentemente isómeros simples como drogas candidatas par evitar cualquier problema farmacológico, farmacocinético y

toxicológico que pudiera surgir debido a las interacciones de un isómero no deseado con objetivos moleculares no deseados. ----------

En este contexto, se podrán preparar estrategias sintéticas para producir isómeros simples puros que ofrecen ventajas sobre las técnicas analíticas de separación de isómero no solamente en términos de costo y eficiencia sino también en cantidades mayores de compuesto par elaborar análisis farmacéutico. De este modo, los compuestos del presente invento, que son isómeros quirales simples, tienen propiedades potenciales mejoradas, farmacocinéticas mejoradas y/o fisico-químicas mejoradas en comparación con los compuestos racémicos. ----------

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El presente invento está dirigido a subsanar problemas encontrados en la técnica. ----------

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Resumen del Invento. ----------

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El presente invento se relaciona con ácidos carboxílicos sustituidos con amino y β-hidroxi, que actúan como inhibidores de la metaloproteasa matriz, especialmente ácidos carboxílicos β-hidroxi diastereoméricamente puros, procesos correspondientes para la síntesis de composiciones farmacéuticas que contienen los compuestos del presente invento. El presente invento se relaciona con inhibidores de la metaloproteinasa matriz útiles como agentes terapéuticos o profilácticos efectivos para el tratamiento

de diversas enfermedades inflamatorias, de autoinmunidad y alérgicas y otros desórdenes inflamatorios caracterizados por la hiper-expresión y la hiper-activación de una metaloproteinasa matriz utilizando los compuestos. --------

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El presente invento se relaciona a compuestos que actúan como inhibidores duales de la MMP-9/12, que tiene perfiles de actividad deseados y potencia beneficiosa, selectividad y/o propiedades farmacocinéticas. ----------

-

El presente invento incluye nuevas entidades químicas que poseen centros quirales como isómeros simples. Se podrán proporcionar estrategias sintéticas para producir isómeros simples puros que ofrecen ventajas sobre las técnicas analíticas de separación de isómeros no solo en términos de costo y eficiencia sino también mayor cantidad de compuesto para elaborar el análisis farmacéutico. ----------

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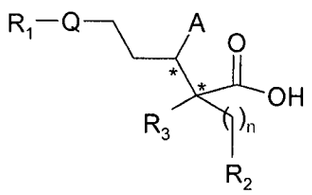
Se especificarán otros aspectos en la descripción que sigue, y en parte resultará evidente de la descripción o podrá aprenderse con la práctica del invento. ----------

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Descripción detallada del Invento. ----------

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El presente invento se relaciona a compuestos que tienen la estructura de la Fórmula I: ----------



Fórmula I

en donde: ----------

* denota o representa un centro estereogénico o asimétrico de configuración definida seleccionado de (R, R), (S, S), (R, S) y (S,R); ----------

n es un entero de 1 a 5; ----------

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

R_2 es heterociclilo, heteroarilo, NR_4R_5, $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$, $C(=Y)NR_4R_5$, $C(=O)OR_6$,

en donde: ----------

Y es oxígeno o azufre, OR_5, $-OC(=O)NR_4R_5$, O-acilo, $S(O)_mR_4$, $-SO_2N(R_4)_2$, ciano, amidino o guanidina; ----------

R_x es R_4 o $-SO_2N(R_4)_2$; ----------

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R_6 es hidrógeno, alquilo, cicloalquilo, aralquilo, heteroarilalquilo, heterociclilalquilo o cicloalquilalquilo ----------

-

en donde: ----------

-

R_4 es alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heterociclilo, heteroarilo, aralquilo, heteroarilalquilo, heterociclilalquilo o cicloalquilalquilo; y ----------

-

m es un entero 0-2; R_5 es hidrógeno o R_4; ----------

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R_3 es hidrógeno, flúor, alquilo, cicloalquilalquilo o aralquilo; ----------

-

A es OH, OR_4, $-OC(=O)NR_4R_5$, O-acilo, NH_2, NR_4R_5, $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$; ----------

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Q es arilo o heteroarilo opcionalmente sustituido. --------

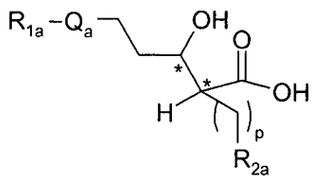
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Los compuestos de la fórmula I tienen propiedades especialmente ventajosas, que podrán incluir actividades biológicas, como por ejemplo modelado de neutrofilia de rata incus-LPS, inhibición selectiva de la actividad de la

MMP-9 y MMP-12, e inhibición de estas actividades sin selectividad hacia la actividad de la MMP-1. Asimismo, estas propiedades ventajosas podrán incluir solubilidades que resaltan la preparación y la administración de formas de dosis, y biodisponibilidad mejorada, en comparación con compuestos conocidos, por ejemplo, aquellos de la WO 2005/026120. -----

En un procedimiento, el invento se relaciona con compuestos de la fórmula general Ia, ----------

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(Ia)

en donde: ----------

-

* denota o representa un centro estereogénico o asimétrico de configuración definida seleccionado de (R, R), (S, S), (R, S) y (S,R); ----------

-

p es un entero de 1 a 3; ----------

-

R_{1a} es arilo o heteroarilo opcionalmente sustituido; ------

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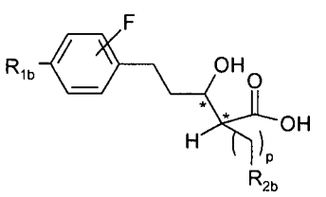
R_{2a} es un heterociclilo de 5-6 miembros que contienen N unido a través del átomo N, que se fusiona opcionalmente al arilo, heteroarilo o se fusiona en forma de espiral al

cicloalquilo, que podrá también ser opcionalmente sustituido con uno o más del grupo oxo, alquilo, cicloalquilo, halo, alcoxi, trifluoroalquilo o arilo; ----------

Q_a es heteroarilo de 5 ó 6 miembros opcionalmente sustituido que contiene 1-3 heteroátomos seleccionados de O, N o S. ---

Los compuestos de la fórmula Ia tienen propiedades especialmente ventajosas, que podrán incluir actividades biológicas, como ser el modelado de neutrofilia de rata incus-LPS, inhibición selectiva de la actividad de la MMP-9 y MMP-12 e inhibición de estas actividades sin selectividad hacia la actividad MMP-1. Asimismo, estas propiedades ventajosas podrán incluir solubilidades que resaltan la preparación y administración de formas de dosis, y biodisponibiliad mejorada, en comparación con compuestos conocidos, por ejemplo, aquellos de la WO 2005/026120. ----

En otro procedimiento, el invento se relaciona con compuestos de la fórmula general Ib, ----------



(Ib)

en donde: ----------

* denota o representa un centro estereogénico o asimétrico de configuración definida seleccionada de (R, R), (S, S), (R, S) y (S,R); ----------

-

p es un entero de 1 a 3; ----------

-

R_{1b} es fenilo o heteroarilo opcionalmente sustituido; en donde los sustituyentes opcionales podrán seleccionarse de uno o más entre alquilo, halo, alcoxi, trifluoroalquilo o arilo; ----------

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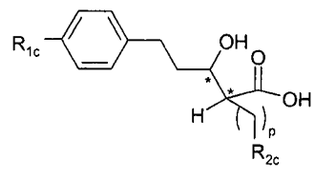
R_{2b} es heterociclilo de 5-6 miembros que contiene N unido a través del átomo N, que se fusiona opcionalmente al arilo, heteroarilo o que se fusiona en forma de espiral al cicloalquilo, que también podrá ser opcionalmente sustituido con uno o más del grupo oxo, alquilo, cicloalquilo, halo, alcoxi, trifluoroalquilo o arilo. ----------

Los compuestos de la fórmula Ib poseen propiedades especialmente ventajosas, que podrán incluir actividades biológicas, como por ejemplo modelado de neutrofilia de rata incus-LPS, inhibición selectiva de la actividad de la MMP-9 y MMP-12, e inhibición de estas actividades sin selectividad hacia la actividad MMP-1. Asimismo, estas propiedades ventajosas podrán incluir solubilidades que resaltan la preparación y administración de formas de dosis, y biodisponibilidad mejorada, en comparación con

compuestos conocidos, por ejemplo, aquellos de la WO 2005/026120. -----

En otro procedimiento, el invento se relaciona con compuestos de la fórmula general Ic, ----------

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(Ic)

en donde: ----------

-

* denota o representa un centro estereogénico o asimétrico de configuración definida seleccionado de (R, R), (S, S), (R, S) y (S,R); ----------

-

p es un entero de 1 a 3; ----------

-

R_{1c} es fenilo, piridilo, pirimidilo, tienilo o pirazolilo opcionalmente sustituido; en donde el sustituyente opcional podrá seleccionarse de uno o más entre alquilo, halo, alcoxi, trifluoroalquilo o arilo; ----------

-

R_{2c} es heterociclilo de 5-6 miembros que contienen N unido a través de un átomo N, que se fusiona opcionalmente al arilo, heteroarilo o que se fusiona en forma de espiral al cicloalquilo, que también podrá sustituise opcionalmente con uno o más del grupo oxo, alquilo, cicloalquilo, halo,

alcoxi, trifluoroalquilo o arilo. ----------

-

En compuestos de la Fórmula Ic, R_{2c} representa heterociclilo de 5-6 miembros que contienen N unido a través del átomo N, que se fusiona opcionalmente al arilo, heteroarilo o se fusiona en forma de espiral al cicloalquilo, por ejemplo benzotriazinona, isoindolediona, pirimidinodiona, aza-spiro[4.5]decanodiona, benzo-oxazinodiona, imidazolidino-diona o ftalazinona. ----------

-

Los compuestos de la fórmula Ic tienen propiedades especialmente ventajosas, que podrán incluir actividades biológicas, como por ejemplo el modelado de neutrofilia de rata incus-LPS, inhibición selectiva de la actividad de la MMP-9 y MMP-12, e inhibición de estas actividades sin selectividad hacia la actividad de la MMP-1. Además, estas propiedades ventajosas podrán incluir solubilidades que resaltan la preparación y la administración de formas de dosis, y biodisponibilidad mejora, en comparación con los compuestos conocidos, por ejemplo, aquellos de la WO 2005/026120. ----------

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También se proporcionan los diastereómeros, isómeros rotativos, óxidos N, polimorfos, sales farmacéuticamente aceptables y solvatos farmacéuticamente aceptables de estos compuestos, prodrogas y metabolitos que tienen el mismo tipo de actividad, como asimismo composiciones farmacéuticas que comprenden los compuestos, sus

metabolitos, diastereómeros, isómeros conformacionales, óxidos N, polimorfos, solvatos o sales farmacéuticamente aceptables de los mismos, en combinación con un conductor farmacéuticamente aceptable y excipientes opcionalmente incluidos. ----------

En un procedimiento, el invento abarca compuestos de la Fórmula (I), que podrán incluir, a modo de ejemplo, lo siguiente, por ejemplo ----------

(2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4H)-il) etil]-5-(4-pirimidin-5-ilfenil)ácido pentanoico (Compuesto Nro.1), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil- 1,3- dioxo -1,3- dihidro -2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4- (6-metoxipiridin-3-il) fenil]ácido pentanoico (Compuesto Nro. 2), ----------

(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]ácido pentanoico (Compuesto Nro. 3), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -(4'-fluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 4), ----------

(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-hidroxi ácido

pentanoico (Compuesto Nro. 5), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]-2- [2-(4-oxo-1,2,3-benzotriazin- 3 (4*H*) -il) etil] ácido pentanoico (Compuesto Nro. 6), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3- dihidro- 2*H*-isoindol-2-il)etil]-5-[4-(6-metilpiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 7), ----------

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(2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1, 3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]ácido pentanoico (Compuesto Nro. 8), ----------

(2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 9), ----------

(2*S*,3*R*)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 10), ----------

(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(5-me-til-1,3-dioxo-1,3-dihidro-2*H*- isoindol -2-il) etil] ácido pentanoico (Compuesto Nro. 11), ----------

(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo -1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico

(Compues-to Nro. 12), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Compues-to Nro. 13), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4'-(trifluorometoxi)bifenil-4-il]ácido pentanoi-co (Compuesto Nro. 14), ----------

(2*S*,3*R*)-5-(4'-cloro-3'-fluorobifenil-4-il)-3-hidroxi-2-[2-(4 -oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 15), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro- 2*H*-isoin-dol-2-il)etil]-5-(3',4'-difluorobifenil-4-il)-3-hidroxi áci-do pentanoico (Compuesto Nro. 16), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro-2*H*- isoin-dol-2-il)etil]-3-hidroxi -5- (4'-metoxibifenil-4-il) ácido pentanoico (Compuesto Nro. 17), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4*H*) -il) etil]-5- [4'- (trifluorometil) bifenil-4-il] ácido pentanoico (Compuesto Nro. 18), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3- dihidro- 2*H*-isoin-dol-2-il) etil]-5- (4'-fluorobifenil-4-il)-3-hidroxi

ácido pentanoico (Compuesto Nro. 19), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro-2*H*-isoin-dol-2-il)etil]-5-(4'-clorobifenil-4-il)-3-hidroxi ácido pen-tanoico (Compuesto Nro. 20), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4'-(trifluorometil)bifenil-4-il]ácido pentanoico (Compuesto Nro. 21), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-(4'-metilbifenil-4-il)ácido pentanoico (Compuesto Nro. 22), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -(3'-fluoro-4'-metoxibifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 23), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il) etil] ácido pentanoico (Compuesto Nro. 24), ----------

(2*S*,3*R*)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 25), ----------

(2*S*,3*R*)-5-(4'-etilbifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico

(Compuesto Nro. 26), ----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1,3 -dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]ácido pentanoico (Compuesto Nro. 27), ----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 28), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-(4-pirimidin-5-ilfenil)ácido pentanoico (Compues-to Nro. 29), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]ácido pentanoi-co (Compuesto Nro. 30), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-(4-piridin-3-ilfenil) ácido pentanoico (Compuesto Nro. 31), ----------

(2*S*,3*R*)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil]- 3-hi-droxi-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4*H*) -il) etil] ácido pentanoico (Compuesto Nro. 32), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido

pentanoi-co (Compuesto Nro. 33), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil] ácido penta-noico (Compuesto Nro. 34), ----------

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(2*S*,3*R*)-3-hidroxi-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 35), ----------

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(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(6-metoxipiridin-3-il)fenil] ácido penta-noico (Compuesto Nro. 36), ----------

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(2*S*,3*R*)-2-[2-(7-cloro-4-oxo-1,2,3- benzotriazin - 3 (4*H*)-il) etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido pen-tanoico (Compuesto Nro. 37), ----------

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(2*S*,3*R*)-3-hidroxi-2-{2-[7-(6-metoxipiridin-3-il)-4-oxo-1,2,3-benzotriazin-3(4*H*)-il]etil}-5-[4-(6-metoxipiridin-3-il) fenil] ácido pentanoico (Compuesto Nro. 38), ----------

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(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 39), ----------

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(2*S*,3*R*)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido

pen-tanoico(Compuesto Nro. 40), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 41), ----------

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(2*S*,3*R*)-3-hidroxi-2-{2-[5-(6-metoxipiridin-3-il)-4-oxo-1,2,3-benzotriazin-3(4*H*)-il]etil}-5-[4-(6-metoxipiridin-3-il)fe-nil] ácido pentanoico (Compuesto Nro. 42), ----------

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(2*S*,3*R*)-5-(4'-cloro-3'-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoi-co (Compuesto Nro. 43), ----------

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(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4-(1-isobutil-1*H*-pirazol-4-il)fenil] ácido pen-tanoico (Compuesto Nro. 44), ----------

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(2*S*,3*R*)-5-bifenil-4-il-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoin-dol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 45), ----------

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(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 46), ----------

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(2*S*,3*R*)-5-(3,3'-difluoro-4'-metoxibifenil-4-il)-2- [2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3- hidroxi

ácido pentanoico (Compuesto Nro. 47), ----------

(2*S*,3*R*)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il) fenil]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi áci-do pentanoico (Compuesto Nro. 48), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4-(1*H*-tetrazol-1-il)fenil] ácido pentanoico (Compuesto Nro. 49), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 50), ----------

(2*S*,3*R*)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(4 -oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 51), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(1-isobutil-1*H*-pirazol-4-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 52), ----------

(2*S*,3*R*)-5-bifenil-4-il-3-hidroxi-2- [2- (4- oxo- 1, 2, 3-benzo-triazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 53), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido

penta-noico (Compuesto Nro. 54), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -[6-(3-fluoro-4-metoxifenil)piridin-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 55), ----------

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(2*S*,3*R*)-5-(4'-cloro-3-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1, 3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 56), ----------

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(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[6-(4-metoxifenil)piridin-3-il] ácido pentanoico (Compuesto Nro. 57), ----------

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(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -(3-fluoro-4'-metoxibifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 58), ----------

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(2*S*,3*R*)-5-[6-(4-clorofenil)piridin-3-il]-2- [2-(1,3-dioxo-1, 3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 59), ----------

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(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il) ácido pentanoico (Compuesto Nro. 60), ----------

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(2*S*,3*R*)-5-[4-(4-clorofenil)-2-tienil]-2- [2- (1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3- hidroxi ácido

pentanoico (Compuesto Nro. 61), ----------

(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)-2-tienil] ácido penta-noico (Compuesto Nro. 62), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-{4-[4-(trifluorometil)fenil]-2-tienil} ácido pen-tanoico (Compuesto Nro. 63), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -[4-(3-fluoro-4-metoxifenil)-2-tienil]-3-hidroxi ácido pen-tanoico (Compuesto Nro. 64), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3 (4*H*)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il] ácido pen-tanoico (Compuesto Nro. 65), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3 (4*H*)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il] ácido pen-tanoico (Compuesto Nro. 66), ----------

(2*S*,3*R*)-2-[2-(7-cloro-4-oxo-1,2,3- benzotriazin -3 (4*H*)-il) etil]-3-hidroxi-5-(4'-metilbifenil-4-il) ácido pentanoico (Compuesto Nro. 67), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3 (4*H*)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il] ácido

pen-tanoico (Compuesto Nro. 68), ----------

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3- benzotriazin-3(4*H*)-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 69), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-[2-fluoro-5-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 70), ----------

(2*S*,3*R*)-5-(4'-cloro-4-fluorobifenil-3-il)-2-[2-(1,3-dioxo-1, 3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 71), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -[6-fluoro-4'-(trifluorometil)bifenil-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 72), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-[4-fluoro-3-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 73), ----------

(2*S*,3*R*)-5-(4'-cloro-6-fluorobifenil-3-il)-2-[2-(1,3-dioxo-1, 3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 74), ----------

(2*S*,3*R*)-5-(3',6-difluoro-4'-metoxibifenil-3-il)-2- [2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi

ácido pentanoico (Compuesto Nro. 75), ----------

(2*S*,3*R*)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin -3 (4*H*) -il) etil]-3-hidroxi-5-(4'-metoxibifenil-4-il) ácido pentanoico (Compuesto Nro. 76), ----------

(2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 77), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(1-metil-1*H*-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 78), ----------

(2*S*,3*R*)-2-[2-(5-cloro-1,3-dioxo-1,3-dihidro-2*H*- isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 79), ----------

(2*S*,3*R*)-2-[2-(4-fluoro-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 80), ----------

(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 81), ----------

(2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4H)-il) etil]-5-fenil ácido pentanoico (Compuesto Nro. 82), ------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-fenil ácido pentanoico (Compuesto Nro. 83), ---

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4(trifluorometil)fenil]ácido pentanoico (Compuesto Nro. 84), ----------

(2*S*,3*R*)-5-(4-*tert*-butilfenil)-2-[2-(1,3-dioxo-1,3-dihidro-2*H* -isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro.85), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3 (4*H*)-il)eti]-5-[4-(1-metil-1*H*-pirazol-4-il)fenil] ácido pen-tanoico (Compuesto Nro. 90), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3 (4*H*)-il)etil]-5-[4-(1-metil-1*H*-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 91), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin- 3 (4H) -il) etil]-5-(3',4'-difluorobifenil-4-il)-3-hidroxi ácido pen-tanoico (Compuesto Nro. 92), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin -3 (4H) -il) etil]-3-hidroxi-5-(4'-metoxibifenil-4-il) ácido pentanoico

(Compuesto Nro. 93), ----------

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(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin -3 (4H) -il) etil]-5-(4'-fluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 94), ----------

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(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil]-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 95), ----------

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(2S,3R)-5-(2',4'-difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 97), ----------

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(2S,3R)-2-[2-(6-cloro-4-oxo-1,2,3-benzotriazin -3 (4H) -il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il) fenil] ácido pentanoico (Compuesto Nro. 98), ----------

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(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin- 3 (4H) -il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 99), ----------

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(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-(4'-isopropilbifenil-4-il) ácido pentanoico (Com-puesto Nro. 100), ----------

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(2S,3R)-5-(3'-cloro-4'-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido penta-

noico (Compuesto Nro. 101), ----------

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(2S,3R)-5-(4'-butilbifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 102), ----------

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(2S,3R)-5-(2'-fluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 103), ----------

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(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin- 3 (4H) -il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il) fenil] ácido pentanoico (Compuesto Nro. 104), ----------

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(2S,3R)-3-hidroxi-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin - 3 (4H)-il)etil]-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 105), ----------

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(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]- 3 -hidroxi-5-{6-[4-(trifluorometil)fenil]piridin-3-il} ácido pentanoico (Compuesto Nro. 106), ----------

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(2S,3R)-5-[6-(3,4-difluorofenil)piridin-3-il]-2-[2-(1,3-dio-xo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido penta-noico (Compuesto Nro. 107), ----------

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(2S,3R)-5-[6-(4-cloro-3-fluorofenil)piridin-3-il]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il) etil] -3- hidroxi

ácido pentanoico (Compuesto Nro. 108), ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[6-(4-fluorofenil)piridin-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 109), ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[6-(3-fluoro-4-metilfenil)piridin-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 110), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il) fenil] ácido pentanoico (Compuesto Nro. 111), ----------

(2S,3R)-2-[2-(8-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il) fenil] ácido pentanoico (Compuesto Nro. 112), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il) fenil] ácido pentanoico (Compuesto Nro. 113), ----------

(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4'-(trifluorometoxi)bifenil-4-il] ácido pentanoico (Compuesto Nro. 114), ----------

(2S,3R)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico

(Com-puesto Nro. 115), ----------

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Com-puesto Nro. 116), ----------

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(7-me-til-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 117), ----------

(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil] ácido penta-noico (Compuesto Nro. 118), ----------

(2S,3R)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil]-3-hi-droxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 119), ----------

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin- 3 (4H) -il) etil]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il) ácido pen-tanoico (Compuesto Nro. 121), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin - 3 (4H) -il) etil]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il) ácido pentanoico (Compuesto Nro. 122), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin -3 (4H)-il)etil]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)

ácido pentanoico (Compuesto Nro. 123), ----------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(7 -metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido penta-noico (Compuesto Nro. 124), ----------

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(2S,3R)-3-hidroxi-5-[4-(1-isobutil-1H-pirazol-4-il)fenil]-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 125), ----------

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(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il) ácido pen-tanoico (Compuesto Nro. 126), ----------

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(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(8-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 127), ----------

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(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2- [2- (8-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido penta-noico (Compuesto Nro. 128), ----------

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(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(8-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 129), ----------

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(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin -3 (4H) -il) etil]-3-hidroxi-5-{6-[4-(trifluorometil)fenil]piridin-3-il}

ácido pentanoico (Compuesto Nro. 130), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin- 3(4H)-il)etil]-3-hidroxi-5-{6-[4-(trifluorometil)fenil]piridin-3-il} ácido pentanoico (Compuesto Nro. 131), ----------

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil]-3-hidroxi-5-{6-[4-(trifluorometil)fenil]piridin-3-il} ácido pentanoico (Compuesto Nro. 132), ----------

(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3- benzotriazin -3 (4H)-il)etil]-5-{6-[4-(trifluorometil) fenil] piridin-3-il} ácido pentanoico (Compuesto Nro. 133), ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil]-3-hidroxi-5-{6-[4-(trifluorometil)fenil] piridin-3-il} ácido pentanoico (Compuesto Nro. 134), ----------

(2S,3R)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-(4'-metilbifenil-4-il) ácido pentanoico (Compuesto Nro. 135), ----------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido penta-noico (Compuesto Nro. 136), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin- 3 (4H)-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il) ácido

pentanoico (Compuesto Nro. 137), ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-(4'-metilbifenil-4-il) ácido pentanoico (Compuesto Nro. 138), ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Com-puesto Nro. 139), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Com-puesto Nro. 140), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido penta-noico (Compuesto Nro. 141), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido penta-noico (Compuesto Nro. 142), ----------

(2*S*,3*S*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Com-puesto Nro. 143), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi

ácido pentanoico (Compuesto Nro. 144), ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(6,7-difluoro-4-oxo-1, 2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 145), ----------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(8 -metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido penta-noico (Compuesto Nro. 146), ----------

(2S,3R)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil]- 3-hi-droxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin- 3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 147), ----------

(2S,3R)-5-[4-(6-cloropiridin-3-il)fenil]-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Com-puesto Nro. 148), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il] ácido pen-tanoico (Compuesto Nro. 149), ----------

(2S,3R)-3-hidroxi-2-[2-(7-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il] ácido pen-tanoico (Compuesto Nro. 150), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-(4'-metilbifenil-4-il) ácido pentanoico

(Compuesto Nro. 151), ----------
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(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(6-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 152), ----------
-

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido penta-noico (Compuesto Nro. 153), ----------
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(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(7-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil] ácido pentanoico (Compuesto Nro. 154), ----------
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(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-2- [2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]- 3 -hidroxi ácido pentanoico (Compuesto Nro. 155), ----------
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(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 156), ----------
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(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 157), ----------
----

(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(7-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico

(Compuesto Nro. 158), ----------

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(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 159), ----------

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(2S,3R)-3-hidroxi-2-[2-(7-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4-(6-metoxipiridin-3-il)fenil] ácido penta-noico (Compuesto Nro. 160), ----------

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(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(7-me-toxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoi-co (Compuesto Nro. 161),----------

----

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4-(6-metoxipiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 162), ----------

-

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]- 3- hidroxi ácido pentanoico (Compuesto Nro. 163), ----------

-

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin -3(4H)-il)etil]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidro-xi ácido pentanoico (Compuesto Nro. 164), ----------

----

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)

300

etil] áci-do pentanoico (Compuesto Nro. 165), ----------

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Com-puesto Nro. 166), ----------

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(2S,3R)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido penta-noico (Compuesto Nro. 167), ----------

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(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 168), ----------

-

(2S,3R)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2- (5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 169), ----------

-

(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2- [2- (5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 170), ----------

-

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(6-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 171), ----------

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(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(6-me-toxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido

pentanoi-co (Compuesto Nro. 172), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4'-(trifluorometoxi)bifenil-4-il] ácido pentanoico (Compuesto Nro. 173), ----------

-

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(6 -metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pen-tanoico (Compuesto Nro. 174), ----------

---

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3- hidroxi ácido pentanoico (Compuesto Nro. 175), ----------

-

(2S,3R)-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)-2-tienil]-2 -[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoi-co (Compuesto Nro. 176), ----------

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(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] áci-do pentanoico (Compuesto Nro. 177), ----------

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(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido penta-noico (Compuesto Nro. 178), ----------

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(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil] ácido penta-

noico (Compuesto Nro. 179), ----------

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(2S,3R)-5-[4-(2-cloropiridin-3-il)fenil]-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 180), ----------

-

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)e-til]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido pen-tanoico (Compuesto Nro. 181), ----------

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(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Com-puesto Nro. 182), ----------

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(2S,3R)-5-(3',4'-difluorobifenil-4-il)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 183), ----------

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(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil]-3-hidroxi-5-(4'-metoxibifenil-4-il) ácido pentanoico (Compuesto Nro. 184), ----------

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(2*S*,3*R*)-3-hidroxi-5-[4-(2-metoxipirimidin-5-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 185), ----------

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(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hi-droxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)

etil] ácido pentanoico (Compuesto Nro. 186), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 187), ----------

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(2*S*,3*R*)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin- 3 (4*H*) -il) etil]-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hidro-xi ácido pentanoico (Compuesto Nro. 188), ----------

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(2*S*,3*R*)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3 (4*H*) -il) etil]-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hidro-xi ácido pentanoico (Compuesto Nro. 189), ----------

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(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 190), ----------

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(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin- 3 (4*H*)-il)etil]-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hi-droxi ácido pentanoico (Compuesto Nro. 191), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 192), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hidroxi-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]

ácido pentanoico (Compuesto Nro. 193), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(2-metoxipirimidin-5-il)fenil] ácido pen-tanoico (Compuesto Nro. 194), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4-(2-metoxipirimidin-5-il)fenil] ácido pentanoi-co (Compuesto Nro. 195), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hi-droxi-2-[2-(1-oxoftalazin-2(1*H*)-il) etil] ácido pentanoico (Compuesto Nro. 196), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hi-droxi-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il) etil] ácido pentanoico (Compuesto Nro. 197), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-{2-[4-oxo-7-(trifluorometil)-1,2,3-benzotriazin-3(4*H*) -il] etil} ácido pentanoico (Compuesto Nro. 198), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(1-oxoftalazin-2(1*H*)-il)etil] ácido pentanoio (Compuesto Nro. 199), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il)etil]

ácido pentanoico (Compuesto Nro. 200), ----------

(2*S*,3*R*)-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-il)etil]-3-hi-droxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 201), ----------

(2*S*,3*R*)-2-[2-(2,4-dioxo-2*H*-1,3-benzoxazin-3(4*H*)-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 202), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(3, 4,4-trimetil-2,5-dioxoimidazolidin-1-il)etil] ácido pen-tanoico (Compuesto Nro. 203), ----------

(2S,3R)-5-(4-cloro-3-fluorofenil)-2-[2-(1,3-dioxo-1,3-dihi-dro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 204), ----------

(2R,3S)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5 -(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 205), ----------

(2*R*,3*S*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -(4'-fluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 206), ----------

(2*R*,3*S*)-5-(3',4'-difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido

pentanoico (Compuesto Nro. 207), ----------

(2*S*,3*S*)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 208), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(5-metilpiridin-2-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 209), ----------

(2*S*,3*R*)-5-[4-(6-fluoropiridin-3-il)fenil]-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 210), ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3 (4H)-il) etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 211), ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 212), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido penta-noico (Compuesto Nro. 213), ----------

(2*S*,3*R*)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico

(Compuesto Nro. 214), ----------

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(2*S*,3*R*)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il) me-til]-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 215), ----------

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(2*S*,3*R*)-5-(2',4'-difluorobifenil-4-il)-3-hidroxi-2- [(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Com-puesto Nro. 216), ----------

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((2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2- [(4-oxo-1,2, 3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Compuesto Nro. 217), ----------

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(2*S*,3*R*)-5-(3'-fluoro-4'-metoxibifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Compuesto Nro. 218), ----------

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(2*S*,3*R*)-3-hidroxi-5-[4-(2-metoxipirimidin-5-il)fenil]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Compuesto Nro. 219), ----------

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(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2- [(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Compuesto Nro. 220), ----------

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(2*S*,3*R*)-3-hidroxi-5-(4'-metilbifenil-4-il)-2- [(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico

(Compuesto Nro. 221), ----------

(2*S*,3*R*)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il) me-til]-5-[4'-(trifluorometoxi)bifenil-4-il] ácido pentanoico (Compuesto Nro. 222), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]-2- [(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Compuesto Nro. 223),----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Compuesto Nro. 224), ----------

(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2- [(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Com-puesto Nro. 225), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-hidroxipiridin-3-il)feni'l]-2-[2-(4 -oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 226), ----------

(2*S*,3*R*)-3-hidroxi-5-(4'-metilbifenil-4-il)- 2- {2- [4-oxo-7-(trifluorometil)-1,2,3-benzotriazin-3(4*H*)-il]etil} ácido pentanoico (Compuesto Nro. 227),----------

(2*S*,3*R*)-2-[2-(2,4-dioxo-1,4-dihidroquinazolin-3(2*H*)-il)etil] -3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido

pentanoi-co (Compuesto Nro. 228), ----------

(2*S*,3*R*)-3-(acetiloxi)-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 229), ----------

(2*S*,3*R*)-2-[2-(8-cloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido pen-tanoico (Compuesto Nro. 230), ----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-2-[2-(2,4-dioxo-2*H*-1,3-ben-zoxazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 231), y ----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-(2-{[(2-hidro-xifenil) carbonil]amino}etil) ácido pentanoico (Compuesto Nro. 232). ----------

En otro procedimiento, el presente invento se relaciona con un auxiliar quiral (4S)-4-bencil-1,3-tiazolidin-2-ona que sería un elemento versátil para la síntesis asimétrica. Los auxiliares quirales se utilizan en una amplia variedad de transformaciones sintéticas que incluyen, a modo de ejemplo, condensación aldol asimétrica, alquilación estereoselectiva, reacción de Diels-Alder estereoselectiva, reacciones de Michael estereoselectivas, diferenciación estereoselectiva de grupos enantiotópicos en moléculas que contienen centros proquirales. El auxiliar quiral se

utiliza en cantidades estoicométricas para inducir la formación estereoselectiva de centros estereogénicos. ----------

En otro procedimiento, el presente invento se relaciona con una dosis terapéuticamente efectiva de un compuesto de la Fórmula I en combinación con uno o más agentes terapéuticos utilizados para tratar diversas enfermedades inflamatorias y alérgicas. Ejemplos de los mencionados agentes terapéuticos incluyen, a modo de ejemplo: ----------

1) Agentes anti-inflamatorios, experimentales o comerciales (i) como por ejemplo agentes anti-inflamatorios no esteroidales piroxicam, diclofenac, ácidos propiónicos, fenamatos, pirazolonas, salicilatos, inhibidores de la Quinasa/Catepsina MAP PDE-4/p38, antagonistas CCR-3, inhibidores iNOS, inhibidores de triptasa y elastasa, antagonistas de integrina beta-2, inhibidores de adhesión celular (especialmente ICAM), agonistas de adenosina 2a (ii) Inhibidores de leucotrienos LTC4/LTD4/LTE4/LTB4-, inhibidores de 5-lipoxigenasas y antagonistas receptores PAF-, (iii) Inhibidores Cox-2 (iv) otros inhibidores de la MMP, (v) inhibidores de interleuquina-I (vi) corticosteroides tales como alclometasona, amcinonida, amelometasona, beclometasona, betametasona, budesonida, ciclesonida, clobetasol, cloticasona, ciclometasona, deflazacort, deprodona, dexbudesonida, diflorasona, difluprednato, fluticasona, flunisolida, halometasona, halopredona,

hidrocortisona, hidrocortisona, metilprednisolona, mometasona, prednicarbato, prednisolona, rimexolona, tixocortol, triamcinolona, ulobetasol, rofleponida, GW 215864, KSR 592, ST-126, dexametasona y las sales farmacéuticamente aceptables, solvatos de los mismos. Los corticosteroides preferidos incluyen, por ejemplo, flunisolida, beclometasona, triamcinolona, budesonida, fluticasona, mometasona, ciclesonida, y dexametasona; -

2) Agonistas-Beta, experimentales o comerciales (i) los agonistas β2 adecuados incluyen, por ejemplo, uno o más de entre albuterol, salbutamol, biltolterol, pirbuterol, levosalbutamol, tulobuterol, terbutalina, bambuterol, metaproterenol, fenoterol, salmeterol, carmoterol, arformoterol, formoterol, y las sales o solvatos farmacéuticamente aceptables de los mismos o se podrán seleccionar más agonistas-β2 de aquellos de la técnica o que se descubran posteriormente. (ii) Los agonistas-β2 podrán incluir uno o más compuestos descriptos en, por ejemplo, las Patentes Norteamericanas Nos. 3,705,233; 3,644,353; 3,642,896; 3,700,681; 4,579,985; 3,994,974; 3,937,838; 4,419,364; 5,126,375; 5,243,076; 4,992,474; y 4,011,258; --------

3) Agentes antihipertensivos, (i) inhibidores ACE, por ej., enalapril, lisinopril, valsartan, telmisartan y quinapril, (ii) antagonistas y agonistas receptores de angiotensina II, por ej., losartan, candesartan, irbesartan, valsartan y eprosartan, (iii) β-

bloqueantes, y (iv) bloqueadores del canal de calcio;

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4) Agentes inmunosupresores, por ejemplo, ciclosporina, azatioprina y metotrexato, corticosteroides anti-inflamatorios; y ----------

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5) Agentes anti-infecciosos (por ej. antibióticos, antivirales). ----------

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DEFINICIONES. ----------

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Las siguientes definiciones se aplican a los términos en la forma que se utilizan en la presente. ----------

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El término "alquilo," salvo que se especifique de otro modo, se refiere a una cadena de hidrocarburo saturada ramificada o no ramificada monoradical que tiene de 1 a 20 átomos de carbono. Los grupos alquilo podrán interrumpirse opcionalmente por átomo(s) o grupo(s) seleccionados independientemente de oxígeno, azufre, un grupo fenileno, sulfinilo, grupo sulfonilo o $-NR_\alpha-$, en donde R_α podrá ser hidrógeno, alquilo, cicloalquilo, alquenilo, cicloalquenilo, alquinilo, arilo, acilo, aralquilo, $-C(=O)OR_\lambda$, SO_mR_ψ o $-C(=O)NR_\lambda R_\pi$. Este término podrá ejemplificarse mediante grupos como ser metilo, etilo, n-propilo, iso-propilo, n-butilo, iso-butilo, sec-butilo, t-butilo, n-pentilo, isopentilo, neopentilo, n-hexilo, n-decilo, tetradecilo, y similares. Los grupos alquilo podrán

sustituirse asimismo con uno o más sustituyentes seleccionados de alquenilo, alquinilo, alcoxi, cicloalquilo, cicloalquenilo, acilo, acilamino, aciloxi, alcoxicarbonilamino, acido, ciano, halógeno, hidroxi, queto, oxo, tiocarbonilo, carboxi, carboxialquilo, arilo, heterociclilo, heteroarilo, (heterociclil)alquilo, cicloalcoxi, -CH=N-O(C_{1-6}alquilo), -CH=N-NH(C_{1-6}alquilo), -CH=N-NH(C_{1-6}alquilo)-C_{1-6}alquilo, ariltio, tiol, alquiltio, ariloxi, nitro, aminosulfonilo, aminocarbonilamino, -NHC(=O)R_λ, -$NR_\lambda R_\pi$, -C(=O)$NR_\lambda R_\pi$, -NHC(=O)$NR_\lambda R_\pi$, -C(=O)heteroarilo, C(=O)heterociclilo, -O-C(=O)$NR_\lambda R_\pi$ {en donde R_λ y R_π se seleccionan independientemente de hidrógeno, halógeno, hidroxi, alquilo, alquenilo, alquinilo, alquenilo, alcoxi, cicloalquilo, cicloalquenilo, arilo, aralquilo, heterociclilo, heteroarilo, heterociclilalquilo, heteroarilalquilo o carboxi}, nitro o -$SO_m R_\psi$ (en donde m es un entero de 0-2 y R_ψ es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, aralquilo, arilo, heterociclilo, heteroarilo, heteroarilalquilo o heterociclilalquilo). Salvo que se restrinja por definición, los sustituyentes alquilo podrán sustituirse por 1-3 sustituyentes seleccionados de alquilo, alquenilo, alquinilo, carboxi, -$NR_\lambda R_\pi$, -C(=O)$NR_\lambda R_\pi$, -OC(=O)$NR_\lambda R_\pi$, -NHC(=O)$NR_\lambda R_\pi$, hidroxi, alcoxi, halógeno, CF_3, ciano, -$SO_m R_\psi$; o también podrá interrumpirse un grupo alquilo por 1-5 átomos de grupos independientemente seleccionados de oxígeno, azufre o -NR_α- (en donde R_α, R_λ, R_π, m y R_ψ son lo definido anteriormente). Salvo que se restrinja de otro modo por la definición, todos los sustituyentes podrán

sustituirse asimismo por 1-3 sustituyentes seleccionados de alquilo, alquenilo, alquinilo, carboxi, carboxialquilo, -$NR_\lambda R_\pi$, -C(=O)$NR_\lambda R_\pi$, -O-C(=O)$NR_\lambda R_\pi$, hidroxi, alcoxi, halógeno, CF_3, ciano, y -$SO_m R_\psi$ (en donde R_λ, R_π, m y R_ψ son lo definido anteriormente); o un grupo alquilo como se define precedentemente tiene ambos sustituyentes en la forma definida con anterioridad y también se interrumpe por 1-5 átomos o grupos como se define precedentemente. ----------

El término "alquenilo," salvo que se especifique de otro modo, se refiere a un grupo monoradical hidrocarburo no saturado ramificado o no ramificado que tiene de 2 a 20 átomos de carbono con geometría cis, trans o geminal. Los grupos alquenilo podrán ser opcionalmente interrumpidos por átomo(s) o grupo(s) independientemente seleccionado de oxígeno, azufre, fenileno, sulfinilo, sulfonilo y -NR_α- (en donde R_α es lo mismo que lo definido anteriormente). En el caso que el alquenilo se anexe a un heteroátomo, la doble unión no podrá ser alfa al heteroátomo. Los grupos alquenilo podrán sustituirse asimismo con uno o más sustituyentes seleccionados de alquilo, alquenilo, alquinilo, alcoxi, cicloalquilo, cicloalquenilo, acilo, acilamino, aciloxi, -NHC(=O)R_λ, -$NR_\lambda R_\pi$, -C(=O)$NR_\lambda R_\pi$, -NHC(=O)$NR_\lambda R_\pi$, -O-C(=O)$NR_\lambda R_\pi$, alcoxicarbonilamino, azido, ciano, halógeno, hidroxi, oxo, queto, carboxialquilo, tiocarbonilo, carboxi, ariltio, tiol, alquiltio, arilo, aralquilo, ariloxi, heterociclilo, heteroarilo, alquil heterociclilo, alquil heteroarilo, aminosulfonilo, aminocarbonilamino, alcoxiamino, hidroxiamino, alcoxiamino,

nitro o SO_mR_ψ (en donde R_λ, R_π, m y R_ψ son lo definido con anterioridad). Salvo que se restrinja de otro modo en la definición, los sustituyentes alquenilo podrán sustituirse opcionalmente también por 1-3 sustituyentes seleccionados de alquilo, alquenilo, alquinilo, carboxi, hidroxi, alcoxi, halógeno, $-CF_3$, ciano, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$ y $-SO_mR_\psi$ (en donde R_λ, R_π, m y R_ψ son lo definido anteriormente). Los grupos, tales como etenilo o vinilo ($CH=CH_2$), 1-propileno o allilo ($-CH_2CH=CH_2$), iso-propileno ($-C(CH_3)=CH_2$), biciclo[2.2.1]hepteno, y similares ejemplifican este término. ----------

El término "alquinilo," salvo que se especifique de otro modo, se refiere a un monoradical de un hidrocarburo no saturado, que tiene de 2 a 20 átomos de carbono. Los grupos alquinilo podrán opcionalmente interrumpirse mediante átomo(s) o grupo(s) independientemente seleccionados de oxígeno, azufre, fenileno, sulfinilo, sulfonilo y $-NR_\alpha-$ (en donde R_α es lo mismo que lo definido anteriormente). En el caso que los grupos alquinilo se anexen a un heteroátomo, la unión triple no podrá ser alfa al heteroátomo. Los grupos alquinilo podrán sustituirse asimismo con uno o más sustituyentes seleccionados de alquilo, alquenilo, alcoxi, cicloalquilo, cicloalquenilo, acilo, acilamino, aciloxi, alcoxicarbonilamino, azido, ciano, halógeno, hidroxi, queto, oxo, tiocarbonilo, carboxi, carboxialquilo, ariltio, tiol, alquiltio, arilo, aralquilo, ariloxi, aminosulfonilo, aminocarbonilamino, hidroxiamino, alcoxiamino, nitro, heterociclilo, heteroarilo, heterociclilalquilo, heteroarilalquilo, $-NHC(=O)R_\lambda$, $-NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, -

$C(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$ or $-SO_mR_\psi$ (en donde R_λ, R_π, m y R_ψ son lo mismo que lo definido con anterioridad). Salvo que se restrinja de otro modo por la definición, los sustituyentes alquinilo podrán opcionalmente sustituirse también mediante 1-3 sustituyentes seleccionados de alquilo, alquenilo, alquinilo, carboxi, carboxialquilo, hidroxi, alcoxi, halógeno, CF_3, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, ciano o $-SO_mR_\psi$ (en donde R_λ, R_π, m y R_ψ son lo mismo que lo definido con anterioridad). ----------

El término "cicloalquilo," salvo que se especifique de otro modo, se refiere a grupos alquilo cíclicos de desde 3 a 20 átomos de carbono que tienen un anillo cíclico simple o anillos condensados múltiples, que podrán contener opcionalmente una o más uniones olefínicas, salvo que se restrinja de otro modo en la definición. Esos grupos cicloalquilo podrán incluir, por ejemplo, estructuras de anillo simples, incluyendo ciclopropilo, ciclobutilo, ciclooctilo, ciclopentenilo, y similares o estructuras de anillo múltiples, incluyendo adamantanilo, y grupos biciclo [2.2.1] heptano o alquilo cíclicos a los cuales se fusiona un grupo arilo, por ejemplo, indano, y similares. Se podrán incluir también las estructuras de anillos en espiral y fusionadas. Los grupos cilcloalquilo podrán sustituirse asimismo con uno o más sustituyentes seleccionados de alquilo, alquenilo, alquinilo, alcoxi, cicloalquilo, cicloalquenilo, acilo, acilamino, aciloxi, alcoxicarbonilamino, azido, ciano, halógeno, hidroxi, oxo, tiocarbonilo, carboxi, carboxialquilo, ariltio, tiol,

alquiltio, arilo, aralquilo, ariloxi, aminosulfonilo, aminocarbonilamino, $-NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-NHC(=O)R_\lambda$, $-C(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$, nitro, heterociclilo, heteroarilo, heterociclilalquilo, heteroarilalquilo o SO_mR_ψ (en donde R_λ, R_π, m y R_ψ son lo mismo que lo definido con anterioridad). Salvo que se restrinja de otro modo por la definición, los sustituyentes cicloalquilo podrán opcionalmente sustituirse asimismo por 1-3 sustituyentes seleccionados de alquilo, alquenilo, alquinilo, carboxi, hidroxi, alcoxi, halógeno, CF_3, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-OC(=O)NR_\lambda R_\pi$, ciano o $-SO_mR_\psi$ (en donde R_λ, R_π, m y R_ψ son lo mismo que lo definido con anterioridad). "Cicloalquilalquilo" se refiere al grupo alquil-cicloalquilo unido a través de una porción alquilo, en donde el alquilo y el cicloalquilo son lo mismo que lo definido con anterioridad. ----------

El término "aralquilo," salvo que se especifique de otro modo, se refiere al alquilo-arilo unido a través de una porción alquilo (en donde el alquilo es lo definido precedentemente) y la porción alquilo contiene 1-6 átomos de carbono y arilo es lo que se define más abajo. Ejemplos de grupos aralquilo incluyen bencilo, etilfenilo, propilfenilo, naftilmetilo y similares. ----------

El término "arilo," salvo que se especifique de otro modo, se refiere a un sistema aromático que tiene 6 a 14 átomos de carbono, en donde el sistema de anillo podrá ser mono-, bi- o tricíclico y son grupos aromáticos carbocíclicos. Por

ejemplo, los grupos arilo incluyen, a modo de ejemplo, anillo fenilo, bifenilo, antrilo o naftilo y similares, sustituidos opcionalmente con 1 a 3 sustituyentes seleccionados de halógneo (por *ej.*, F, Cl, Br, I), hidroxi, alquilo, alquenilo, alquinilo, cicloalquilo, alcoxi, acilo, ariloxi, CF_3, ciano, nitro, $COOR_\psi$, $NHC(=O)R_\lambda$, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$, $-SO_mR_\psi$, carboxi, heterociclilo, heteroarilo, heterociclilalquilo, heteroarilalquilo o amino carbonil amino, mercapto, haloalquilo, arilo opcionalmente sustituido, heterociclilalquilo opcionalmente sustituido, tioalquilo, $-CONHR_\pi$, $-OCOR_\pi$, $-COR_\pi$, $-NHSO_2R_\pi$ o $-SO_2NHR_\pi$ (en donde R_λ, R_π, m y R_ψ son lo mismo que lo definido con anterioridad). Los grupos arilo opcionalmente podrán fusionarse con un grupo cicloalquilo, en donde el grupo cicloalquilo podrá contener opcionalmente heteroátomos seleccionados de O, N o S. Los grupos tales como fenilo, naftilo, antrilo, bifenilo, y similares ejemplifican este término. ----------

El término "*ariloxi*" denota el grupo O-arilo en donde el arilo es lo mismo que lo definido precedentemente. --------

El término "heteroarilo," salvo que se especifique lo contrario, se refiere a una estructura de anillo aromático que contiene 5 ó 6 átomos en anillo o un grupo aromático bicíclico o tricíclico que tiene de 8 a 10 átomos en anillo, con uno o más heteroátomo(s) seleccionados independientemente de N, O o S opcionalmente sustituidos con 1 a 4 sustituyente(s) seleccionados de halógeno (por

ej., F, Cl, Br, I), hidroxi, alquilo, alquenilo, alquinilo, cicloalquilo, acilo, carboxi, arilo, alcoxi, aralquilo, ciano, nitro, heterociclilo, heteroarilo, $-NR_\lambda R_\pi$, CH=NOH, $-(CH_2)_wC(=O)R_\eta$ {en donde w es un entero de 0-4 y R_η es hidrógeno, hidroxi, OR_λ, $NR_\lambda R_\pi$, $-NHOR_\omega$ o -NHOH}, $-C(=O)NR_\lambda R_\pi$ $-NHC(=O)NR_\lambda R_\pi$, $-SO_mR_\psi$, $-O-C(=O)NR_\lambda R_\pi$, $-O-C(=O)R_\lambda$, o $-O-C(=O)OR_\lambda$ (en donde m, R_ψ, R_λ y R_π son lo definido anteriormente y R_ω es alquilo, cicloalquilo, arilo, heteroarilo, heterociclilo, heteroarilalquilo o heterociclilalquilo). Salvo que se restrinja de otro modo por la defínción, los sustituyentes se anexan a un átomo en anillo, *es decir*, carbono o 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, piracinilo, tienilo, isoxazolilo, triacinilo, furanilo, benzofuranilo, indolilo, benztiacinilo, benztiacinonilo, benzoxacinilo, benzoxacinonilo, quinazonilo, carbazolilo, fenotiacinilo, fenoxacinilo, benzotiazolilo o benzoxazolilo, y similares. -

El término "heterociclilo," salvo que se especifique de otro modo, se refiere a un grupo cicloalquilo monocíclico o bicíclico no aromático que tiene 5 a 10 átomos en donde 1 a 4 átomos de carbono de un anillo se reemplazan por heteroátomos seleccionados de O, S o N, y opcionalmente resultan benzofusionados o heretoarilo fusionados teniendo 5-6 miembros en el anillo y/o se sustituyen opcionalmente, en donde los sustituyentes se seleccionan de halógeno (por

ej., F, Cl, Br, I), hidroxi, alquilo, alquenilo, alquinilo, cicloalquilo, acilo, arilo opcionalmente sustituido, alcoxi, alcarilo, ciano, nitro, oxo, carboxi, heterociclilo opcionalmetne sustituido, heterociclilalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -O-C(=O)Rλ, -O-C(=O)ORλ, -C(=O)NRλRπ, SOmRψ, -O-C(=O)NRλRπ, -NHC(=O)NRλRπ, -NRλRπ, mercapto, haloalquilo, tioalquilo, -COORψ, -COONHRλ, -CORλ, -NHSO2Rλ o SO2NHRλ (en donde m, Rψ, Rλ y Rπ son lo definido con anterioridad) o guanidina. El heterociclilo podrá incluir opcionalmente anillos que tienen uno o más uniones dobles. Esos sistemas de anillo podrán ser mono-, bi- o tricíclicos. El grupo carbonilo o sulfonilo podrá reemplazar átomo(s) de carbono del heterociclilo. Salvo que se restrinja de otro modo en la definición, los sustituyentes se anexan al átomo en el anillo, *es decir*, carbono o heteroátomo en el anillo. Asimismo, salvo que se restrinja de otro modo en la definición, el anillo heterociclilo podrá contener opcionalmente una o más unión(es) olefínica(s). Ejemplos de grupos heterociclilos incluyen benzotriazinona, isoindolediona, pirimidinadiona, aza-spiro[4.5]decanediona, benzo-oxacinediona, imidazolidinadiona, ftalacinona, oxazolidinilo, tetrahidrofuranilo, dihidrofuranilo, benzoxacinilo, benztiacinilo, imidazolilo, bencimidazolilo, tetrazolilo, carbaxolilo, indolilo, fenoxacinilo, fenotiacinilo, dihidropiridinilo, dihidroisoxazolilo, dihidrobenzofurilo, azabiciclohexilo, tiazolidinilo, dihidroindolilo, piridinilo, isoindol 1,3-diona, piperidinilo, tetrahidropiranilo, piperacinilo, 3H-

imidazo[4,5-b]piridina, isoquinolinilo, 1H-pirrolo[2,3-b]piridina o piperacinilo y similares. ----------

El término "*cicloalquilalquilo*" se refiere a un grupo cicloalquilo unido a través de la porción alquilo, en donde el alquilo que tiene 1 a 6 átomos de carbono y cicloalquilo son lo mismo que lo definido con anterioridad. ----------

El término "*Heteroarilalquilo*" se refiere a un grupo heteroarilo unido a través de la porción alquilo, en donde el alquilo que tiene 1 a 6 átomos de carbono y heteroarilo son lo mismo que lo definido con anterioridad. ----------

El término "*Heterociclilalquilo*" se refiere al grupo heterociclilo unido a través de la porción alquilo, en donde el alquilo que tiene 1 a 6 átomos de carbono y heterociclilo son lo mismo que lo definido con anterioridad. ----------

El término "*amino*" se refiere a $--NH_2$ ----------

El término "*acilo*" se refiere a $-C(=O)R_4$ en donde R_4 es lo mismo que lo definido con anterioridad. ----------

El término "*tioacilo*" se refiere a $-C(=S)R_4$ en donde R_4 es lo mismo que lo definido con anterioridad; ----------

El término "*halógeno*" se refiere a fluor, cloro, bromo o yodo; ----------

El término "grupo saliente" se refiere a grupos que exhiben o potencialmente exhiben las propiedades de ser inestables en las condiciones sintéticas y también, de ser rápidamente separados de productos sintéticos conforme a las condiciones definidas. Ejemplos de grupos salientes incluyen, a modo de ejemplo, halógeno (por *ej.*, F, Cl, Br, I), triflatos, tosilato, mesilatos, alcoxi, tioalcoxi, o radicales hidroxi y similares. ----------

El término "grupos protectores" se refiere a porciones que evitan la reacción química en una ubicación de una molécula que se pretende dejar desafectada durante la modificación química de esa molécula. Salvo que se especifique lo contrario, los grupos protectores podrán utilizarse sobre grupos, como ser hidroxi, amino o carboxi. Ejemplos de grupos protectores se encuentran en *T.W. Greene y P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd Ed., John Wiley and Sons*, Nueva York, N.Y., que se incorpora a la presente por referencia. Las especies de los grupos protectores carboxílicos, grupos protectores amino o grupos protectores hidroxi empleados no son críticos, en la medida que las porciones/la porción derivada sea/sean estables en condiciones de reacciones posteriores y puedan ser removidos sin desorganizar el resto de la molécula. ----------

Los compuestos descriptos en la presente podrán contener uno o más átomos de carbono asimétricos y de este modo pasar como diastereómeros. Estos compuestos también podrán existir como confórmeros/rotámeros. Todas esas formas isoméricas de estos compuestos se incluyen en la presente. Cada carbono estereogénico podrá ser de la configuración *R* o *S*. Aunque los compuestos específicos ejemplificados en esta solicitud podrán ilustrarse en una configuración estereoquímica particular, se preveen los compuestos que tienen ya sea la estereoquímica opuesta en cualquier centro quiral dado o las mezclas de los mismos. ----------

El término "*sales farmacéuticamente aceptables*" que forman parte de este invento incluyen las sales de la porción de ácido carboxílico, que podrán prepararse reaccionando el compuesto con la base apropiada para proporcionar las sales de adición base correspondientes. Ejemplos de esas bases son hidróxido de metal álcali incluyendo hidróxido de potasio, hidróxido de sodio e hidróxido de litio; hidróxidos metálicos de tierra alcalina como ser hidróxido de magnesio e hidróxido de calcio. Asimismo las sales de bases orgánicas como ser lisina, arginina, guanidina, etanolamina, colina y similares; bases inorgánicas por ej., amoníaco o sales de amoníaco sustituidas también se encuentran incluidos. En donde resultare apropiado, los compuestos del presente invento también podrán formar las sales de adición ácidas tratando esos compuestos con ácidos orgánicos e inorgánicos farmacéuticamente aceptables, por ej., hidrohaluros como ser clorhidrato, bromhidrato,

yodohidrato; otros ácidos minerales y sus sales correspondientes como ser sulfato, nitrato, fosfato, etc.; y alquilo y mono-arilsulfonatos como ser etanosulfonato, toluenosulfonato y bencenosulfonato; y otros ácidos orgánicos y sus sales correspondientes como ser acetato, tartarato, maleato, succinato, citrato, etc. ------

Las formas de sales difieren del compuesto descripto en la presente en diversas propiedades físicas como ser solubilidad, pero las sales de otro modo resultan equivalentes para el objeto de este invento. ----------
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El término "solvatos *farmacéuticamente aceptables*" se refiere a solvatos con agua (es decir, hidratos) o solventes farmacéuticamente aceptables, por ejemplo solvatos con etanol y similares. Los mencionados solvatos también están comprendidos dentro del alcance de la revelación. Asimismo, algunas formas cristalinas para los compuestos descriptos en la presente podrán existir como *polimorfos* y como tales se apunta a incluirlos en el alcance de la revelación. --------

El término "polimorfos" incluye todas las formas cristalinas como asimismo las formas amorfas para los compuestos descriptos en la presente y como tal se incluyen en el presente invento. ----------
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La frase "conductores farmacéuticamente aceptables" apunta a incluir material no tóxico, sólido inerte, semi-sólido o líquido de relleno, diluyente, de encapsulación o auxiliar

de formulación de cualquier tipo. ----------

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El término "farmacéuticamente aceptable" significa aprobado por la agencia regulatoria del gobiero federal o de un estado, o enumerado en la Farmacopea de los EE.UU. u otras farmacopeas comúnmnente reconocidas para uso en animales, y más especialmente en seres humanos. ----------

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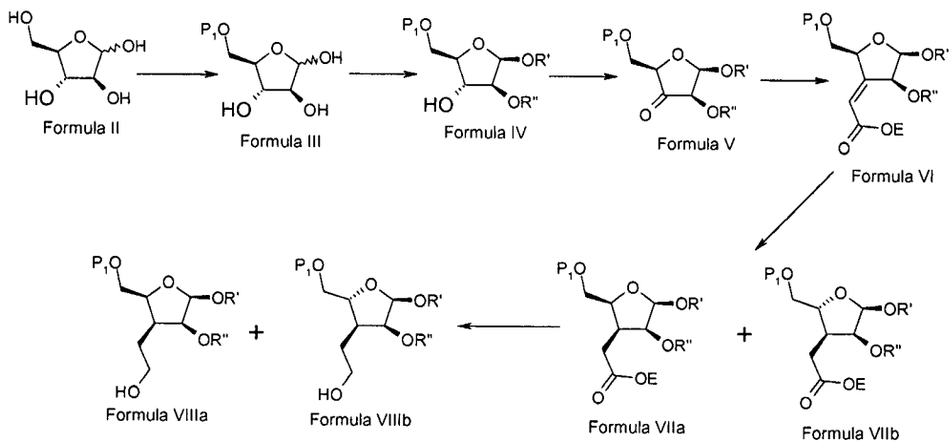
Ejemplos de estados inflamatorios y desórdenes de autoinmunidad en los cuales los compuestos del invento tienen potencialmente efectos beneficiosos en métodos de tratamiento podrán incluir, a modo de ejemplo, enfermedades del tracto respiratorio como por ejemplo asma (incluyendo reacciones asmáticas inducidas por alergenos), fibrosis cística, bronquitis (incluyendo bronquitis crónica), enfermedad pulmonar obstructiva crónica (COPD), síndrome de perturbación respiratoria en adultos (ARDS), inflamación pulmonar crónica, rinitis y desórdenes inflamatorios del tracto respiratorio superior (URID), lesión pulmonar inducida por ventilación, silicosis, sarcoidosis pulmonar, fibrosis pulmonar idiopática, displasia broncopulmonar, artritis, por *ej.*, artritis reumatoidea, osteoartritis, atritis infecciosa, artritis soriásica, artritis traumática, artritis rubéola, síndrome de Reiter, artritis gotosa y falta de articulación protésica, gota, sinovitis aguda, espondilitis y estados inflamatorios no articulares, por *ej.*, síndrome de disco intervertebral con hernia /quebrado / con prolapso, bursitis, tendinitis, tenosinovitis, síndrome fibromiálgico y demás estados

inflamatorios asociados con luxación de ligamentos y tono musculoeaquelético regional, desórdenes inflamatorios del tracto gastrointestinal, por *ej.*, colitis ulcerativa, diverticulitis, enfermedad de Crohn, enfermedades intestinales inflamatorias, síndrome intestinal irritable y gastritis, esclerosis múltiple, lupus eritematoso sistémico, escleroderma, exocrinopatía de autoinmunidad, encefalomietilis autoinmune, diabetes, tumor de angiogénesis y metástasis, cáncer incluyendo carcinoma de mamas, colon, recto, pulmón, riñón, ovario, estómago, útero, páncreas, hígado, oral, laríngeo y de 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, hernia inguinal, degeneración retinal, retinopatía diabética, degeneración macular, inflamación ocular, enfermedades de reabsorción ósea, osteoporosis, osteopetrosis, reacción injerto contra huésped, rechazos de transplantes, sepsis, endotoxemia, síndrome de shock tóxico, tuberculosis, neumonía organizativa intersticial y criptogénica común, meningitis bacteriana, caquexia sistémica, caquexia secundaria a infección o maliciosa, caquexia secundaria a síndrome de inmunodeficiencia adquirido (AIDS), malaria, lepra, leishmaniasis, enfermedad de Lyme, glomerulonefritis, glomeruloesclerosis, fibrosis renal, fibrosis de hígado, pancreatitis, hepatitis, endometriosis, dolor, por *ej.*, asociadas con la inflamación y/o trauma, las enfermedades

inflamatorias de la piel, por ej, dermatitis, dermatosis, úlceras dérmicas, psoriasis, eczema, vasculitis sistémica, demencia vascular, trombosis, ateroesclerosis, restenosis, lesión de reperfusión, placa de calcificación, miocarditis, aneurisma, ataque apopléjico, hipertensión pulmonar, remodelación del ventrículo izquierdo e insuficiencia cardíaca. Aquellos imbuidos en la técnica apreciarán que la referencia del presente al tratamiento se extiende a la profilaxis como asimismo al tratamiento de estados establecidos. ----------

Los compuestos revelados en la presente podrán prepararse, por ejemplo, mediante técnicas bien conocidas en la síntesis orgánica y familiares para aquellos comúnmente imbuidos en la técnica de este invento. Además, los procesos descriptos en la presente podrán permitir la síntesis de los compuestos del presente invento. No obstante, estos no serán los únicos medios por medio de los cuales podrán sintetizarse los compuestos descritps en el invento. Asimismo, las diversas etapas sintéticas descriptas en la presente podrán realizarse en secuencias alternadas con el fin de proporcionar los compuestos deseados. ----------

Scheme-I



Los compuestos de las Fórmulas VIIIa y VIIIb podrán prepararse siguiendo, por ejemplo, las rutas sintéticas que se describen en el Esquema I. De este modo, un compuesto de la Fórmula II podrá convertirse en un compuesto de la Fórmula III (en donde P_1 es un grupo protector sililo, por ejemplo, *tert*-butildimetilsilano, *tert*-butildifenilsilano o triisopropilsilano), que luego podrá convertirse en un compuesto de la Fórmula IV (en donde P_1 se define como en la forma precedente, R' y R" juntos forman un grupo protector acetal, por ejemplo, isopropilideno o ciclohexilideno acetal). El compuesto de la Fórmula IV podrá oxidizarse para formar un compuesto de la Fórmula V. El compuesto de la Fórmula V luego podrá convertirse en un compuesto de la Fórmula VI (en donde E es un grupo alquilo tal como metilo, etilo y similares), que luego podrán hidrogenarse para formar compuestos de las Fórmulas VIIa y VIIb. Los compuestos de las Fórmulas VIIa y VIIb podrán reducirse para formar compuestos de las Fórmulas VIIIa y VIIIb. ----------

Se podrá realizar la sililación de un compuesto de la Fórmula II para formar un compuesto de la Fórmula III con reactivos sibilantes como ser, por ejemplo, tert-butildimetilclorosilano, trifenilclorosilano, t-butil-difenilclorosilano ante la presencia de una base, por ejemplo, imidazol o trietilamina en un solvente orgánico, por ejemplo, dimetil formamida, dimetilsulfóxido o acetonitrilo. ----------

Se podrá realizar la acetonación de un compuesto de la Fórmula III para formar un compuesto de la Fórmula IV con acetona en exceso como un solvente, ante la presencia de un catalizador ácido suave, por ejemplo, anhidrido de cobre (II) sulfato y ácido canforsulfónico, anhídrido de cloruro de zinc y una pequeña cantidad de ácido fosfórico, o cloruro férrico anhidro. Se podrá utilizar alternativamente trans-acetonación con dimetoxipropano ante la presencia de catalizadores ácidos como ser ácido p-toluenosulfónico, ácido sulfúrico o montmorillonita-K. ----------

El compuesto de la Fórmula IV podrá oxidizarse para formar un compuesto de la Fórmula V, por ejemplo, utilizando oxidación *Swern* (Dimetilsulfóxido y cloruro de oxalilo) u oxidación de *Corey-Kim* (N-clorosuccinimida y Dimetilsulfuro) ante la presencia de una base, por ejemplo, trietilamina, diisopropiletilamina ante un solvente, por ejemplo, diclorometano o tolueno. Alternativamente, el compuesto de la Fórmula IV podrá oxidizarse en un compuesto de la Fórmula V en, por ejemplo, diclorometano o cloroformo

con un agente oxidizante, como ser el reactivo de *Dess-Martin*, clorocromato de piridinio (PCC) o dicromato de piridinio (PDC). La oxidación del compuesto de la Fórmula IV para formar un compuesto de la Fórmula V también podrá realizarse catalíticamente utilizando, por ejemplo, 2,2,6,6,-tetrametilpiperidina N-oxilo (TEMPO) y los derivados 4-sustituidos del mismo, incluyendo, por ejemplo, 4-metoxi-TEMPO, 4-etoxi-TEMPO, 4-acetoxi-TEMPO, 4-acetamino-TEMPO, 4-hidroxi-TEMPO, 4-benzoiloxi-TEMPO, 4-amino-TEMPO, N,N-dimetilamino-TEMPO, o 4-oxo-TEMPO como catalizador, ante la presencia de un co-catalizador, por ejemplo, bromuro de potasio o bromuro de sodio, con un oxidante, por ejemplo, hipoclorito de sodio, hipoclorito de potasio, hipoclorito de calcio, hipodromito de sodio o hipodromito de potasio en un solvente, por ejemplo, cloruro de metileno, cloroformo, acetado de etilo, acetato de butilo, acetonitrilo, tetrahidrofurano, tolueno, acetona, éter dietilo, éter metilo tert-butilo, pentano, hexano o mezclas de los mencionados solventes. ----------

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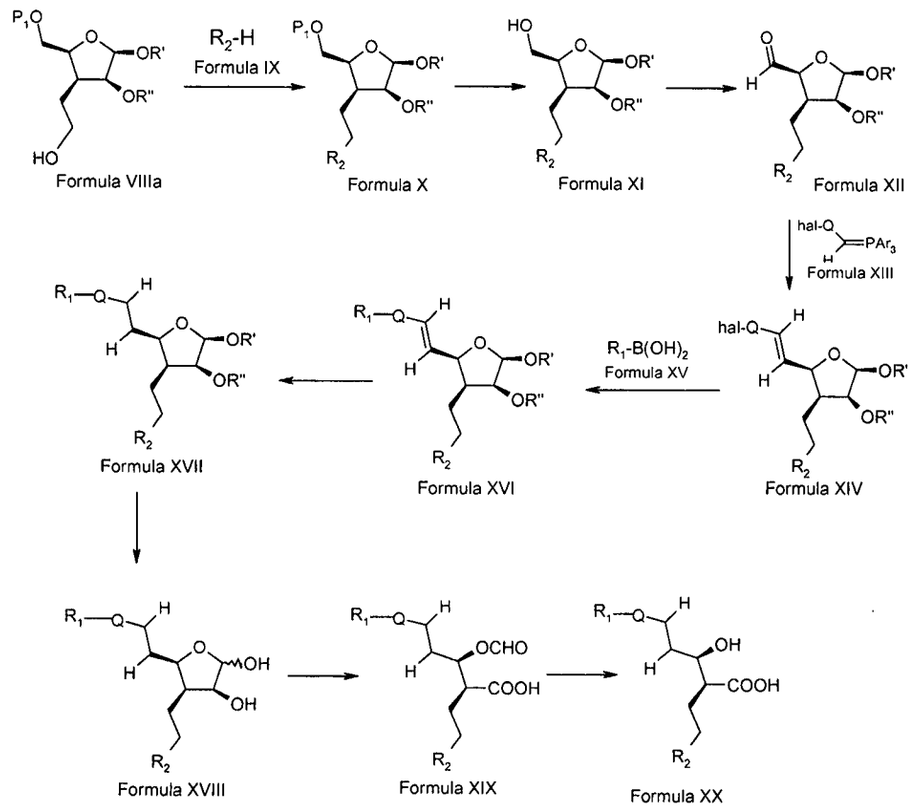
El compuesto de la Fórmula V podrá convertirse en un compuesto de la Fórmula VI, por ejemplo, a través de la reacción *Horner-Wadsworth-Emmons*, así un compuesto de la Fórmula V podrá reaccionar con fosfonato carbaniones (producidos *in situ* mediante tratamiento de trimetilfosfonoacetato o trietilfosfonoacetato con una base, por ejemplo, hidruro de sodio, hidruro de potasio, tert-butóxido de potasio, tert-butóxido de sodio, carbonato de potasio, trietilamina en un solvente orgánico, por

ejemplo, tetrahidrofurano o dimetoxietano para dar un compuesto de la Fórmula VI. Alternativamente, la reacción de *Wittig* podrá ser realizada utilizando el reactivo preformado de *Wittig* tal como (carboetoximetileno)-trifenilfosforano. ----------

Podrá llevarse a cabo la hidrogenación de un compuesto de la Fórmula VI para formar compuestos de las Fórmulas VIIa y VIIb con paladio sobre carbono ante la presencia de hidrógeno, en un solvente adecuado, por ejemplo, metanol, etanol, propanol, tetrahidrofurano, acetato de etilo o mezcla(s) de los mismos. ----------
-

Los compuestos de las Fórmulas VIIa y VIIb podrán reducirse para dar compuestos de las Fórmulas VIIIa y VIIIb ante la presencia de un agente reductor, por ejemplo, hidruro de aluminio litio, borohidruro trietilo de litio o borohidruro de sodio, ante la presencia de un aditivo, por ejemplo, cloruro de litio o cloruro de aluminio, en un solvente orgánico, por ejemplo, tetrahidrofurano, dietiléter o diglime. ----------
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Scheme-II



Los compuestos de la Fórmula XX podrán prepararse, por ejemplo, siguiendo las rutas sintéticas ilustradas en el Esquema II. De este modo, un compuesto de la Fórmula VIIIa (en donde P_1, R' y R'' son lo mismo que lo definido con anterioridad), podrán reaccionar con un compuesto de la Fórmula IX (en donde R_2 es un heterociclilo que contiene N- o un heteroarilo) para dar un compuesto de la Fórmula X. El compuesto de la Fórmula X podrá sufrir desprotección para formar un compuesto de la Fórmula XI que ante la oxidación podrá dar un compuesto de la Fórmula XII. El compuesto de la Fórmula XII al reaccionar con un compuesto de la Fórmula XIII (en donde Q es lo mismo que lo definido con anterioridad, hal es Cl, Br o I y Ar es fenilo) podrá formar un compuesto de la Fórmula XIV. El compuesto de la

Fórmula XIV luego podrá reaccionar con un compuesto de la Fórmula XV (en donde R_1 es lo mismo que lo definido anteriormente) para formar un compuesto de la Fórmula XVI que podrá luego hidrogenarse para formar un compuesto de la Fórmula XVII. El compuesto de la Fórmula XVII podrá sufrir desprotección para formr un compuesto de la Fórmula XVIII que después podrá dividirse oxidativamente para formar un compuesto de la Fórmula XIX. El compuesto de la Fórmula XIX podrá desformilarse para formar un compuesto de la Fórmula XX. ---

La reacción del compuesto de la Fórmula VIIIa con un compuesto de la Fórmula IX para dar un compuesto de la Fórmula X podrá llevarse a cabo utilizando trifenilfosfina o tributilfosfina y azodicarboxilato dietilo, azodicarboxilato diisoproil o 1,1'-azodicarbonildipiperidina en un solvente orgánico, por ejemplo, tetrahidrofurano, dimetilformamida o tolueno. ----

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El compuesto de la Fórmula X podrá desprotegerse para formar un compuesto de la Fórmula XI con agentes desprotectores, por ejemplo, fluoruro de tetrabutilamoníaco o fluoruro de potasio en un solvente orgánico, por ejemplo, tetrahidrofurano, dimetilformamida, éter dietilo o dioxano, opcionalmente ante la presencia de éteres corona como ser, por ejemplo, 18-corona-6. La oxidación de un compuesto de la Fórmula XI para dar un compuesto de la Fórmula XII podrá realizarse similarmente como la conversión de un compuesto de la Fórmula IV para formar un compuesto de la Fórmula V. -

El compuesto de la Fórmula XII podrá convertirse en un compuesto de la Fórmula XIV reaccionando con un compuesto de la Fórmula XIII (reactivo de *Wittig, es decir*, un ilido, preparado mediante reacción de una sal de fosfonio, a su vez preparada de trifenilfofina y haluro alquilo, en un solvente por ejemplo, tetrahidrofurano, dimetilo sulfóxido o éter dietilo, con una base fuerte, por ejemplo, n-butillito, hidruro de sodio o potasio tert-butóxido). ----------

La reacción de un compuesto de la Fórmula XIV con un compuesto de la Fórmula XV podrá llevarse a cabo ante la presencia de un catalizador metálico, por ejemplo, tetraquis (trifenilfosfina) paladio (0), tetraquis (triciclohexilfosfna) paladio (0), tetraquis (tri-tert-butilfosfina) paladio (0) o acetato de paladio y trifenilfosfina ante la presencia de una base por ejemplo, carbonato de potasio o carbonato de cesio, en un solvente orgánico, por ejemplo, tolueno, dimetilo sulfóxido, dimetilformamida, tetrahidrofurano, dioxano o éter dietilo.

La hidrogenación de un compuesto de la Fórmula XVI para formar un compuesto de la Fórmula XVII podrá realizarse similarmente como conversión de un compuesto de la Fórmula VI a compuestos de las Fórmulas VIIa y VIIb. ----------

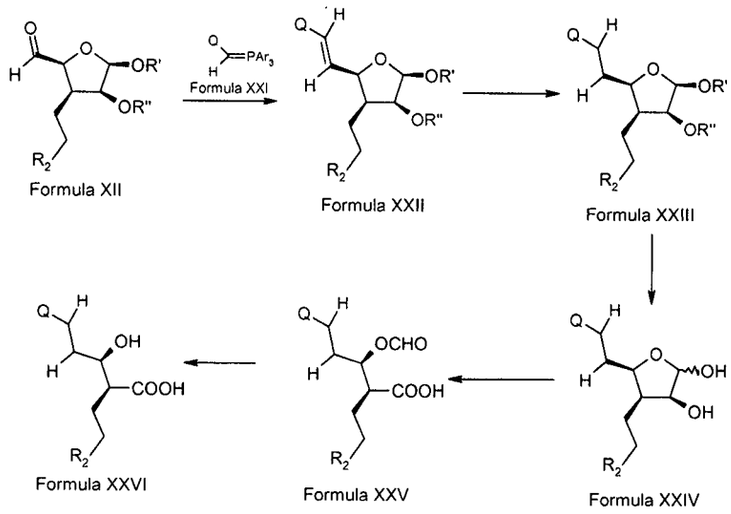
El compuesto de la Fórmula XVII podrá desprotegerse para formar un compuesto de la Fórmula XVIII con ácido perclórico, ácido acético o ácido clorhídrico en solvente(s), por ejemplo, acetonitrilo, agua,

tetrahidrofurano o mezcla(s) de los mismos. ----------
-

La conversión de un compuesto de la Fórmula XVIII para formar un compuesto de la Fórmula XIX podrá realizarse mediante división diol ante la presencia de, por ejemplo, metaperiodato de sodio, tetraacetato de plomo, clorocromato de piridinio o dióxido de manganeso, en co-solventes, por ejemplo, tert-butanol-agua, metanol-tetrahidrofurano o tert-butanol-tetrahidrofurano, seguido de oxidación con, por ejemplo, permangnato de potasio o con una mezcla de fosfato dihidrogenado de sodio, clorito de sodio y peróxido de hidrógeno. ----------
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El compuesto de la Fórmula XIX podrá desformilarse para formar un compuesto de la Fórmula XX ante la presencia de una base por ejemplo, carbonato de potasio, carbonato de sodio o trietilamina en un solvente, por ejemplo, metanol, tetrahidrofurano o mezcla(s) de los mismos. ----------
-

Scheme-III



Los compuestos de la Fórmula XXVI podrán prepararse mediante las siguientes rutas sintéticas, por ejemplo, como se ilustra en el Esquema III. De este modo, un compuesto de la Fórmula XII podrá reaccionar con un compuesto de la Fórmula XXI (en donde Q es lo mismo que lo definido anteriormente y Ar es fenilo) para formar un compuesto de la Fórmula XXII (en donde R_2 es un heterociclilo o heteroarilo que contiene N-), que asimismo podrá hidrogenarse para formar un compuesto de la Fórmula XXIII. El compuesto de la Fórmula XXIII podrá desprotegerse para formar un compuesto de la Fórmula XXIV, que luego podrá dividirse oxidativamente para dar un compuesto de la Fórmula XXV. El compuesto de la Fórmula XXV podrá luego desformilarse para formar un compuesto de la Fórmula XXVI.

La reacción de un compuesto de la Fórmula XII con un compuesto de la Fórmula XXI para formar un compuesto de la Fórmula XXII podrá realizarse similarmente como conversión

de un compuesto de la Fórmula XII en un compuesto de la Fórmula XIV. La hidrogenación de un compuesto de la Fórmula XXII para dar un compuesto de la Fórmula XXIII podrá realizarse en condiciones similares como las de la conversión del compuesto de la Fórmula VI en compuestos de las Fórmulas VIIa y VIIb.----------

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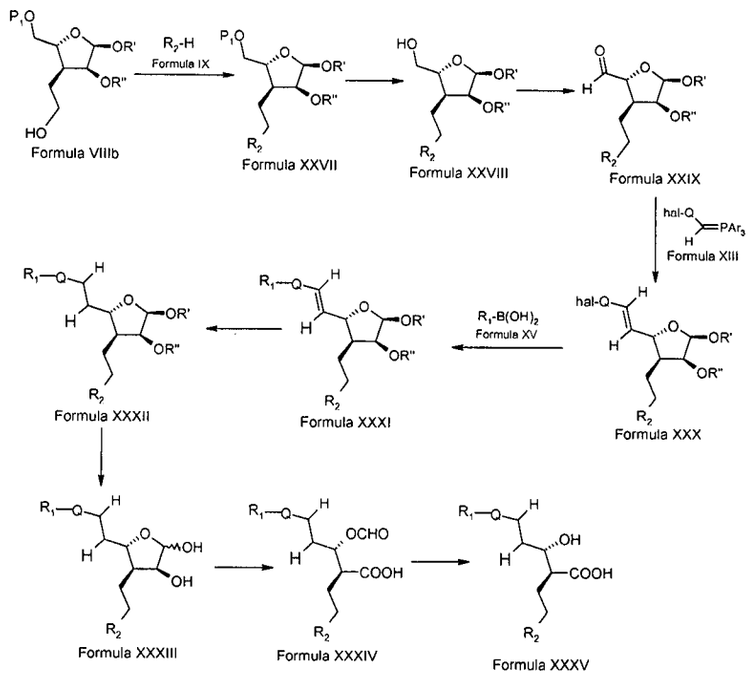
La desprotección de un compuesto de la Fórmula XXIII para dar un compuesto de la Fórmula XXIV podrá realizarse similarmente como conversión de un compuesto de la Fórmula XVII en un compuesto de la Fórmula XVIII. La división oxidativa de un compuesto de la Fórmula XXIV para formar un compuesto de la Fórmula XXV podrá realizarse en condiciones similares a las de conversión de un compuesto de la Fórmula XVIII en un compuesto de la Fórmula XIX. ----------

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La desformilación de un compuesto de la Fórmula XXV para formar un compuesto de la Fórmula XXVI podrá realizarse similarmente a la conversión de un compuesto de la Fórmula XIX para dar un compuesto de la Fórmula XX. ----------

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Scheme-IV



Los compuestos de la Fórmula XXXV podrán prepararse, por ejemplo, siguiendo las rutas sintéticas ilustradas en el Esquema IV. De este modo, un compuesto de la Fórmula VIIIb (en donde P_1, R' y R'' son lo mismo que lo definido con anterioridad), podrá reaccionar con un compuesto de la Fórmula IX (en donde R_2 es un heterociclilo o heteroarilo que contiene N- para dar un compuesto de la Fórmula XXVII. El compuesto de la Fórmula XXVII podrá desprotegerse para formar un compuesto de la Fórmula XXVIII, que ante la oxidación dará un compuesto de la Fórmula XXIX. El compuesto de la Fórmula XXIX ante la reacción con un compuesto de la Fórmula XIII podrá formar un compuesto de la Fórmula XXX que luego podrá reaccionar con un compuesto de la Fórmula XV (en donde R_1 es lo mismo que lo definido con anterioridad) para formar un compuesto de la Fórmula XXXI. El compuesto de la Fórmula XXXI podrá luego

hidrogenarse para formar un compuesto de la Fórmula XXXII que después podrá sufrir desprotección para formar un compuesto de la Fórmula XXXIII. El compuesto de la Fórmula XXXIII podrá dividirse oxidativamente para formar un compuesto de la Fórmula XXXIV. El compuesto de la Fórmula XXXIV luego podrá desformilarse para formar un compuesto de la Fórmula XXXV. ----------

La reacción de un compuesto de la Fórmula VIIIb con un compuesto de la Fórmula IX para dar un compuesto de la Fórmula XXVII podrá realizarse similarmente como en la conversión de un compuesto de la Fórmula VIIIa para formar un compuesto de la Fórmula X. ----------

La desprotección de un compuesto de la Fórmula XXVII para dar un compuesto de la Fórmula XXVIII podrá realizarse similarmente como la desprotección de un compuesto de la Fórmula X para formar un compuesto de la Fórmula XI. ------

La oxidación de un compuesto de la Fórmula XXVIII para dar un compuesto de la Fórmula XXIX podrá realizarse similarmente como en la conversión de un compuesto de la Fórmula IV para formar un compuesto de la Fórmula V. ------

La reacción de un compuesto de la Fórmula XXIX con un compuesto de la Fórmula XIII para formar un compuesto de la Fórmula XXX podrá realizarse en condiciones similares a las de la conversión de un compuesto de la Fórmula XII para

formar un compuesto de la Fórmula XIV. ----------
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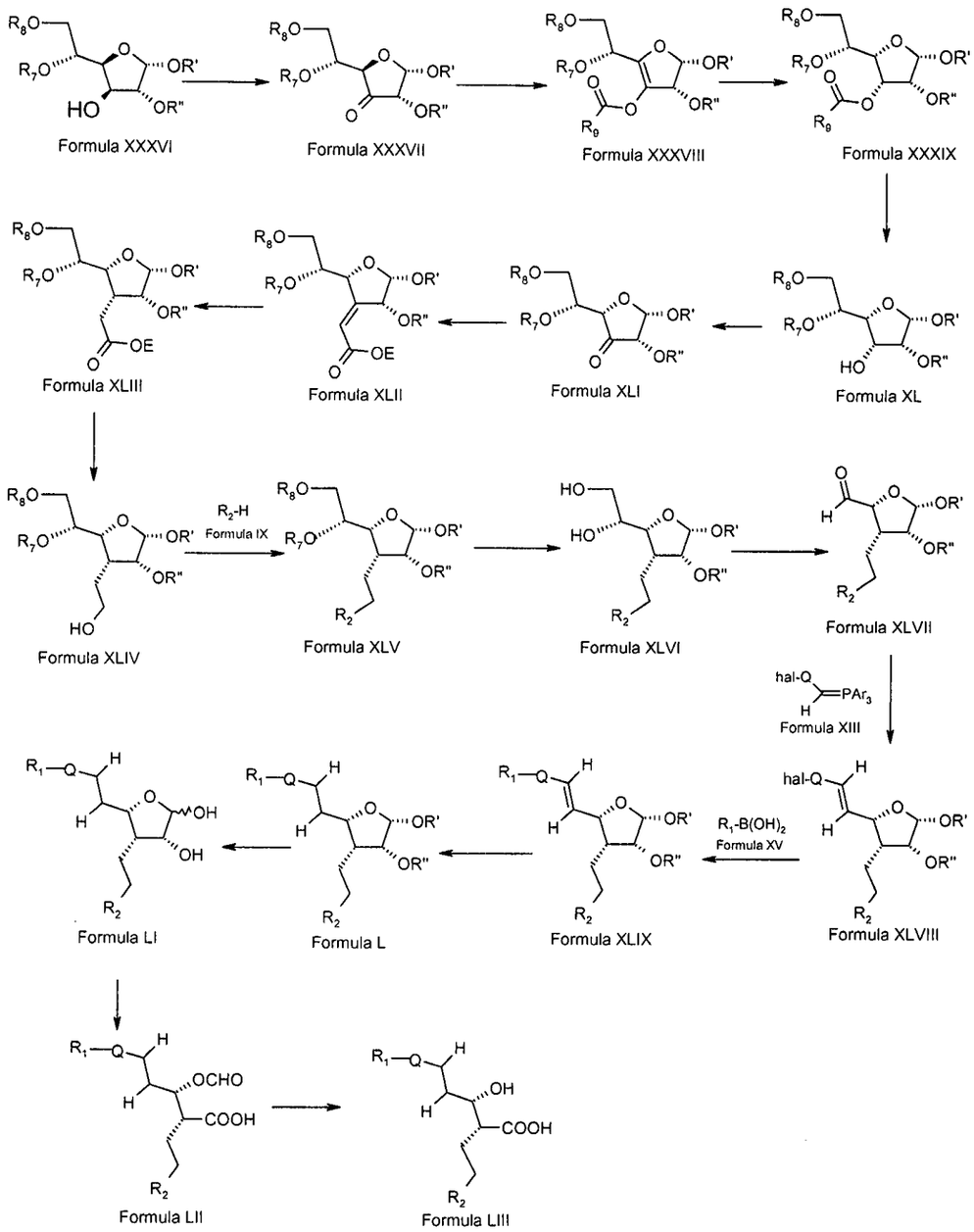
El acomplamiento de un compuesto de la Fórmula XXX con un compuesto de la Fórmula XV para formar un compuesto de la Fórmula XXXI podrá realizarse similarmente a la conversión de un compuesto de la Fórmula XIV para formar un compuesto de la Fórmula XVI. ----------
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La hidrogenación de un compuesto de la Fórmula XXXI para formar un compuesto de la Fórmula XXXII podrá realizarse similarmente como conversión de un compuesto de la Fórmula VI para formar un compuesto de las Formulas VIIa y VIIb. El compuesto de la Fórmula XXXII podrá desprotegerse para formar un compuesto de la Fórmula XXXIII en condiciones similares a las de conversión de un compuesto de la Fórmula XVII para formar un compuesto de la Fórmula XVIII. --------
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La división oxidativa de un compuesto de la Fórmula XXXIII para formar un compuesto de la Fórmula XXXIV podrá realizarse similarmente como la conversión de un compuesto de la Fórmula XVIII para dar un compuesto de la Fórmula XIX.

La desformilación de un compuesto de la Fórmula XXXIV para formar un compuesto de la Fórmula XXXV podrá realizarse en condiciones similares a las de conversión de un compuesto de la Fórmula XIX para formar un compuesto de la Fórmula XX. --

Scheme-V



Los compuestos de la Fórmula LIII podrán prepararse, por ejemplo, siguiendo las rutas sintéticas que se ilustran en el Esquema V. De este modo, un compuesto de la Fórmula XXXVI (en donde R_7 y R_8 juntos forman un grupo protector acetal, por ejemplo, acetal isopropilideno, R' y R" son lo

mismo que lo descripto con anterioridad) podrán oxidizarse para formar un compuesto de la Fórmula XXXVII que luego podrá convertirse para formar un compuesto de la Fórmula XXXVIII (en donde R_9 es alquilo o arilo). El compuesto de la Fórmula XXXVIII podrá hidrogenarse para dar un compuesto de la Fórmula XXXIX que luego podrá hidrolizarse para dar un compuesto de la Fórmula XL. El compuesto de la Fórmula XL podrá oxidizarse para dar un compuesto de la Fórmula XLI que luego podrá convertirse para formar un compuesto de la Fórmula XLII. El compuesto de la Fórmula XLII podrá hidrogenarse para formar un compuesto de la Fórmula XLIII que luego podrá reducirse para formar un compuesto de la Fórmula XLIV. El compuesto de la Fórmula XLIV después podrá reaccionarse con un compuesto de la Fórmula IX (en donde R_2 es un heterociclilo o heteroarilo que contiene N-) para obtener un compuesto de la Fórmula XLV que después podrá desprotegerse para formar un compuesto de la Fórmula XLVI. El compuesto de la Fórmula XLVI podrá oxidizarse para formar un compuesto de la Fórmula XLVII que luego podrá reaccionar con un compuesto de la Fórmula XIII para formar un compuesto de la Fórmula XLVIII. El compuesto de la Fórmula XLVIII después podrá reaccionarse con un compuesto de la Fórmula XV (en donde R_1 es lo mismo que lo definido con anterioridad) para dar un compuesto de la Fórmula XLIX que luego podrá hidrogenarse para formar un compuesto de la Fórmula L. El compuesto de la Fórmula L se deprotegerá para formar un compuesto de la Fórmula LI que después podrá dividirse oxidativamente para formar un compuesto de la Fórmula LII. El compuesto de la Fórmula LII luego se

desformilará para formar un compuesto de la Fórmula LIII. ----------

La oxidación de un compuesto de la Fórmula XXXVI para formar un compuesto de la Fórmula XXXVII podrá realizarse en condiciones similares a las de oxidación de un compuesto de la Fórmula IV para formar un compuesto de la Fórmula V. El compuesto de la Fórmula XXXVII podrá convertirse en un compuesto de la Fórmula XXXVIII ante la presencia de, por ejemplo, anhídrido acético o anhídrido benzoico ante la presencia de una base, como por ejemplo, piridina, trietilamina o morfolina. ----------

El compuesto de la Fórmula XXXVIII podrá hidrogenarse para formar un compuesto de la Fórmula XXXIX similarmente como en la hidrogenación de un compuesto de la Fórmula VI para dar compuestos de las Fórmulas VIIa y VIIb. La hidrólisis de un compuesto de la Fórmula XXXIX para formar un compuesto de la Fórmula XL podrá realizarse con una base, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio o metóxido de sodio ante la presencia de un solvente, por ejemplo, metanol, etanol o isopropanol. El compuesto de la Fórmula XL podrá oxidizarse para formar un compuesto de la Fórmula XLI similarmente al de la conversión de un compuesto de la Fórmula IV para formar un compuesto de la Fórmula V. ----------

La conversión de un compuesto de la Fórmula XLI para formar un compuesto de la Fórmula XLII podrá realizarse en

condiciones similares a las de conversión de un compuesto de la Fórmula V para formar un compuesto de la Fórmula VI. El compuesto de la Fórmula XLII podrá hidrogenarse para formar un compuesto de la Fórmula XLIII similarmente al de la conversión de un compuesto de la Fórmula VI en compuestos de las Fórmulas VIIa y VIIb. La reducción de un compuesto de la Fórmula XLIII para formar un compuesto de la Fórmula XLIV podrá realizarse en condiciones similares a las de la reducción de compuestos de las Fórmulas VIIa y VIIb para formar compuestos de las Fórmulas VIIIa y VIIIb. La reacción de un compuesto de la Fórmula XLIV con un compuesto de la Fórmula IX para formar un compuesto de la Fórmula XLV podrá realizarse similarmente a la de la conversión de un compuesto de la Fórmula VIIIa para formar un compuesto de la Fórmula X. ----------

La desprotección de acetonida selectiva de un compuesto de la Fórmula XLV para formar un compuesto de la Fórmula XLVI podrá realizarse con ácido perclórico en un solvente, por ejemplo, tetrahidrofurano o éter dietilo o ácido trifluoroacético en diclorometano. La oxidación de un compuesto de la Fórmula XLVI para formar un compuesto de la Fórmula XLVII podrá realizarse con, por ejemplo, metaperiodato de sodio, tetraacetato de plomo, clorocromato de piridinio o dióxido de manganeso en un solvente, por ejemplo, acetona, metanol, etanol o tert-butanol. ---------

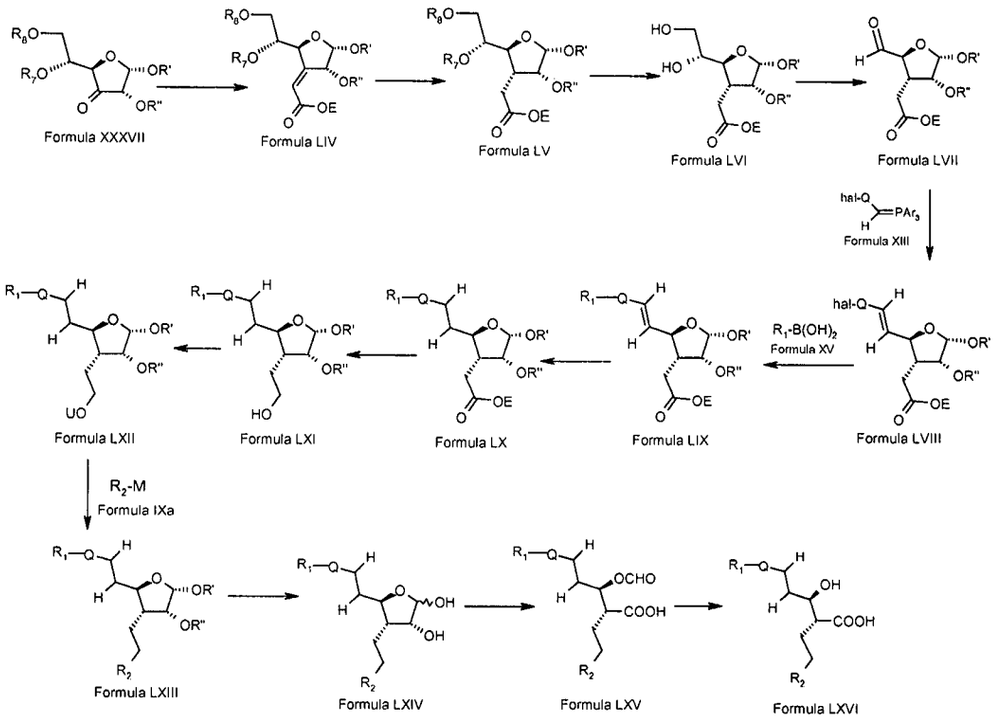
La reacción de un compuesto de la Fórmula XLVII con un compuesto de la Fórmula XIII para formar un compuesto de la

Fórmula XLVIII podrá realizarse similarmente a la de la conversión de un compuesto de la Fórmula XII para formar un compuesto de la Fórmula XIV. El acoplamiento de un compuesto de la Fórmula XLVIII con un compuesto de la Fórmula XV para formar un compuesto de la Fórmula XLIX podrá realizarse similarmente a la conversión de un compuesto de la Fórmula XIV para formar un compuesto de la Fórmula XVI. El compuesto de la Fórmula XLIX podrá hidrogenarse para formar un compuesto de la Fórmula L en condiciones similares a las de la conversión del compuesto de la Fórmula VI en compuestos de las Fórmulas VIIa y VIIb. La desprotección de un compuesto de la Fórmula L para dar un compuesto de la Fórmula LI podrá realizarse en condiciones similares a las de la conversión de un compuesto de la Fórmula XVII para formar un compuesto de la Fórmula XVIII. ----------

La división oxidativa de un compuesto de la Fórmula LI para formar un compuesto de la Fórmula LII podrá realizarse similarmente a la de la conversión de un compuesto de la Fórmula XVIII para formar un compuesto de la Fórmula XIX. El compuesto de la Fórmula LII podrá desformilarse en un compuesto de la Fórmula LIII en condiciones similares a las de la conversión de compuestos de la Fórmula XIX para formar un compuesto de la Fórmula XX. ----------

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Scheme-VI



Los compuestos de la Fórmula LXVI podrán prepararse, por ejemplo, siguiendo las rutas sintéticas como se ilustra en el Esquema VI. De este modo, un compuesto de la Fórmula XXXVII (en donde R_7, R_8, R' y R" son lo mismo que lo descripto anteriormente) podrán convertirse para formar un compuesto de la Fórmula LIV que podrá hidrogenarse para formar un compuesto de la Fórmula LV. El compuesto de la Fórmula LV podrá desprotegerse selectivamente para formar un compuesto de la Fórmula LVI que ante la oxidación, podrá formar un compuesto de la Fórmula LVII. El compuesto de la Fórmula LVII podrá reaccionar con un compuesto de la Fórmula XIII para formar un compuesto de la Fórmula LVIII que después podrá acoplarse con un compuesto de la Fórmula XV (en donde R_1 es lo mismo que lo definido con anterioridad) para dar un compuesto de la Fórmula LIX. El

compuesto de la Fórmula LIX podrá hidrogenarse para formar un compuesto de la Fórmula LX que luego se reducirá para formar un compuesto de la Fórmula LXI. El compuesto de la Fórmula LXI podrá activarse para formar un compuesto de la Fórmula LXII (en donde U es un gruvo activador O-, por ejemplo, mesilo, tosilo o triflato), que después podrán reaccionarse con un compuesto de la Fórmula IXa (en donde R_2 es un heterociclilo o heteroarilo que contiene N- y M es un metal, por ejemplo, potasio, litio o sodio) para formar un compuesto de la Fórmula LXIII. El compuesto de la Fórmula LXIII podrá luego desprotegerse para formar un compuesto de la Fórmula LXIV que podrá dividirse oxidativamente para formar un compuesto de la Fórmula LXV. El compuesto de la Fórmula LXV podrá desformilarse para formar un compuesto de la Fórmula LXVI. -

El compuesto de la Fórmula XXXVII podrá convertirse para formar un compuesto de la Fórmula LIV en condiciones similares a las de la conversión de un compuesto de la Fórmula V para formar un compuesto de la Fórmula VI. La hidrogenación de un compuesto de la Fórmula LIV para formar un compuesto de la Fórmula LV podrá realizarse en forma similar a la de la conversión de un compuesto de la Fórmula VI para formar compuestos de las Fórmulas VIIa y VIIb. ----

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El compueto de la Fórmula LV podrá desprotegerse en forma selectiva de un compuesto de la Fórmula LVI en condiciones similares a las de la conversión de un compuesto de la Fórmula XLV para dar un compuesto de la Fórmula XLVI. El compuesto de la Fórmula LVI podrá oxidizarse para formar un

compuesto de la Fórmula LVII similarmente al de la conversión de un compuesto de la Fórmula XLVI para formar un compuesto de la Fórmula XLVII. ----------

La reacción de un compuesto de la Fórmula LVII con un compuesto de la Fórmula XIII para formar un compuesto de la Fórmula LVIII podrá realizarse en condiciones similares a las de la conversión de un compuesto de la Fórmula XII para formar un compuesto de la Fórmula XIV. El compuesto de la Fórmula LVIII podrá acoplarse con un compuesto de la Fórmula XV para dar un compuesto de la Fórmula LIX en condiciones similares a las de la conversión de un compuesto de la Fórmula XIV para formar un compuesto de la Fórmula XVI. La hidrogenación de un compuesto de la Fórmula LIX para formar un compuesto de la Fórmula LX podrá realizarse en condiciones similares a las de la conversión de un compuesto de la Fórmula VI para formar compuestos de las Fórmulas VIIa y VIIb. ----------

El compuesto de la Fórmula LX podrá reducirse para formar un compuesto de la Fórmula LXI en condiciones similares a las de la conversión del compuesto de las Fórmulas VIIa y VIIb para formar compuestos de las Fórmulas VIIIa y VIIIb. -----

Se podrá activar un compuesto de la Fórmula LXI para formar un compuesto de la Fórmula LXII en un solvente, por ejemplo, diclorometano, tolueno o dicloroetano, utilizando una base, por ejemplo, trietilamina, diisopropilamina o

metilmorfolina-N, utilizando un cloruro de sulfonilo adecuado, por ejemplo, cloruro de metanosulfonilo o cloruro de sulfonilo p-tolueno. La reacción de un compuesto de la Fórmula LXII con un compuesto de la Fórmula IXa para producir un compuesto de la Fórmula LXIII podrá realizarse en un solvente orgánico, por ejemplo, tetrahidrofurano, sulfóxido de dimetilo, dimetilformamida, acetonitrilo, dioxano, dimetilacetamida. Alternativamente, se podrá realizar la reacción de un compuesto de la Fórmula LXII con un compuesto de la Fórmula IX para producir un compuesto de la Fórmula LXIII ante la presencia de una base, por ejemplo, hidruro de sodio, Pert-butóxido de potasio, (m)etóxido de sodio en un solvente orgánico, por ejemplo, tetrahidrofurano, sulfóxido de dimetilo, dimetilformamida, acetonitrilo, dioxano, o dimetilacetamida. Alternativamente, se podrá convertir un compuesto de la Fórmula LXI en un compuesto de la Fórmula LXIII siguiendo protocolos similares a los de la reacción de un compuesto de la Fórmula VIIIa con un compuesto de la Fórmula IX para dar un compuesto de la Fórmula X. ----------

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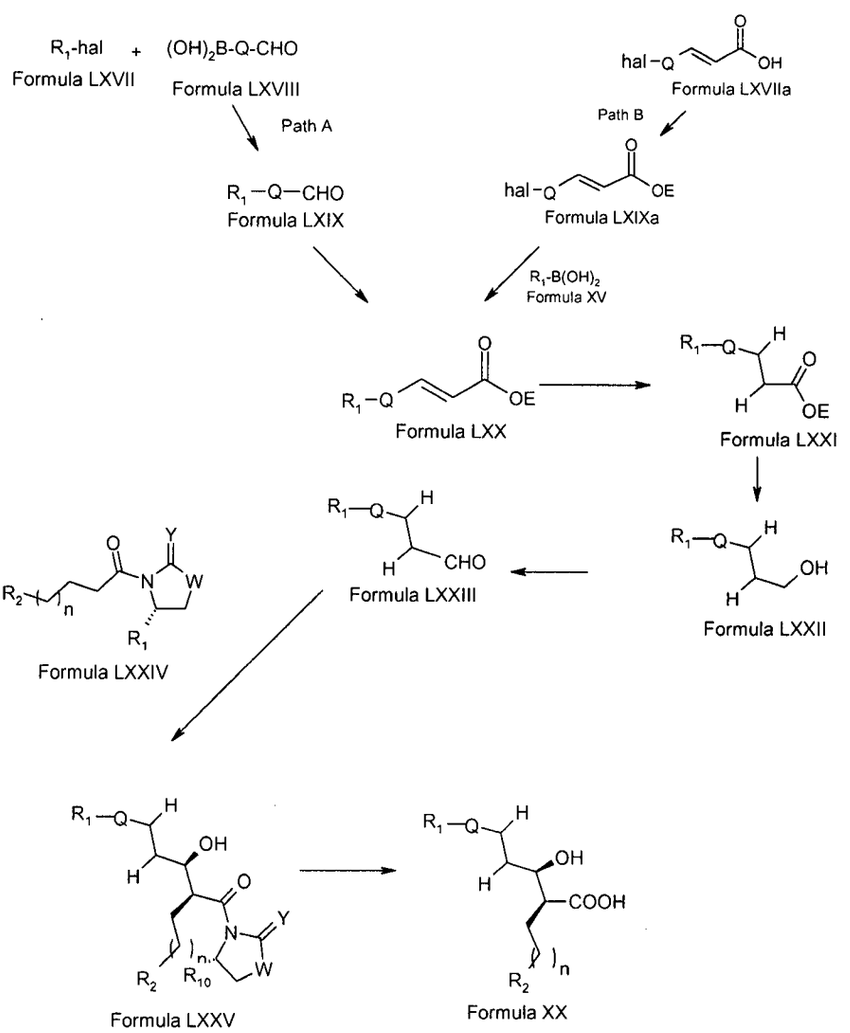
El compuesto de la Fórmula LXIII podrá desprotegerse para formar un compuesto de la Fórmula LXIV en forma similar a la de la conversión de un compuesto de la Fórmula XVII para formar un compuesto de la Fórmula XVIII. ----------

-

Se podrá realizar la división oxidativa de un compuesto de la Fórmula LXIV para dar un compuesto de la Fórmula LXV similarmente a la de la conversión de un compuesto de la

Fórmula XVIII para formar un compuesto de la Fórmula XIX. Se podrá desformilar el compuesto de la Fórmula LXV para formar un compuesto de la Fórmula LXVI en condiciones similares a las de la conversión de un compuesto de la Fórmula XIX para formar un compuesto de la Fórmula XX. ----------

Scheme-VII



Los compuestos de la Fórmula XX también podrán prepararse, por ejemplo, siguiendo las rutas sintéticas alternadas que ilustra el Esquema VII. De este modo, un compuesto de la

Fórmula LXVII podrá acoplarse con un compuesto de la Fórmula LXVIII para formar un compuesto de la Fórmula LXIX (en donde R_1 y Q son lo mismo que lo definido anteriormente), que luego podrá convertirse en un compuesto de la Fórmula LXX (Camino A)(en donde E es lo mismo que lo definido con anterioridad). Alternativamente, el compuesto de la Fórmula LXVIIIa podrá sufrir esterificación para dar un compuesto de la Fórmula LXIXa, que se acoplará con un compuesto de la Fórmula XV para formar un compuesto de la Fórmula LXX (Camino B) (en donde E es lo mismo que lo definido con anterioridad). El compuesto de la Fórmula LXX podrá hidrogenarse para formar un compuesto de la Fórmula LXXI, que luego podrá reducirse para formar un compuesto de la Fórmula LXXII. El compuesto de la Fórmula LXXII podrá oxidizarse para formar un compuesto de la Fórmula LXXIII, que luego podrá reaccionarse con un compuesto de la Fórmula LXXIV (en donde, cuando R_2 es heterociclilo o heteroarilo que contiene N-, Y y W podrán ser oxígeno o azufre, R_{10} podrá ser alquilo, arilo o aralquilo y n es lo definido con anterioridad) para formar un compuesto de la Fórmula LXXV. El compuesto de la Fórmula LXXII asimismo podrá hidrolizarse para formar un compuesto de la Fórmula XX. ---

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El acoplamiento de un compuesto de la Fórmula LXVII con un compuesto de la Fórmula LXVIII para formar un compuesto de la Fórmula LXIX podrá realizarse similarmente como en la conversión de un compuesto de la Fórmula XIV para formar un compuesto de la Fórmula XVI. ---

-

La conversión de un compuesto de la Fórmula LXIX para formar un compuesto de la Fórmula LXX podrá realizarse en condiciones similares a las de la conversión de un compuesto de la Fórmula V para formar un compuesto de la Fórmula VI. La esterificación de un compuesto de la Fórmula LXVIIIa para dar un compuesto de la Fórmula LXIXa podrá realizarse en un solvente, por ejemplo, metanol, etanol, tert-butanol o alcohol bencilo con un agente halogenante, por ejemplo, cloruro de tionilo o cloruro de oxalilo. El acoplamiento de un compuesto de la Fórmula LXIXa con un compuesto de la Fórmula XV para formar un compuesto de la Fórmula LXX podrá realizarse similarmente a la conversión de un compuesto de la Fórmula XIV para formar un compuesto de la Fórmula XVI. -

El compuesto de la Fórmula LXX podrá hidrogenarse para formar un compuesto de la Fórmula LXXI en forma similar al de la conversión de un compuesto de la Fórmula VI en compuestos de las Fórmulas VIIa y VIIb. Se podrá realizar la reducción de un compuesto de la Fórmula LXXI para formar un compuesto de la Fórmula LXXII en condiciones similares a las de la reducción de compuestos de las Fórmulas VIIa y VIIb para formar compuestos de las Fórmulas VIIIa y VIIIb. Se podrá oxidizar el compuesto de la Fórmula LXXII para formar un compuesto de la Fórmula LXXIII en forma similar al de la oxidación de un compuesto de la Fórmula IV para formar un compuesto de la Fórmula V. ----------

El agregado de aldol asimétrico de un compuesto de la Fórmula LXXIII con un compuesto de la Fórmula LXXIV para

formar un compuesto de la Fórmula LXXIV podrá realizarse generando los enolatos con cloruro de titanio, triflato de boron dibutilo, cloruro de boron dialquilo o trifalto de estaño(II), ante la presencia de una base, por ejemplo, diisopropiletilamina, tetrametiletelenodiamina, tributil-amina, N-etilpiperidina, 1,4-diazabiciclo [2.2.2] octano, 1,8-Diazabiciclo[5.4.0]undec-7-eno, tetrametilpropileno-diamina, o (-) esparteina, en un solvente, por ejemplo, diclorometano, o éter dietilo. ----------

Se podrá realizar la hidrólisis de un compuesto de la Fórmula LXXIV para formar un compuesto de la Fórmula XX con peróxido de hidrógeno e hidróxido de litio, ante la presencia de un solvente, por ejemplo, tetrahidrofurano, agua o mezcla(s) de los mismos. ----------

Los compuestos Nros. 1 to 81, 86-88, 90-95, 97-119, 121-142, 144-203, 211-213 y 226-232 se prepararon siguiendo los Esquemas I y II. Los compuestos Nros. 82 a 85, y 204 se prepararon siguiendo los Esquemas I, II y III. Los compuestos Nros. 143, y 208 se prepararon siguiento el Esquema IV. Los compuestos Nros. 120, y 205-207 Se prepararon siguiento el Esquema V. Los compuestos Nros. 89, y 96 se prepararon siguiendo el Esquema VI. Los compuestos Nros. 86, 209-210 y 214-225 Se prepararon siguiendo el Esquema VII. ----------

En los esquemas precedentes, donde se mencionan bases, ácidos, solventes, agentes condensadores, agente reductor, agente desprotector, agentes hidrolizantes, catalizadores metálicos específicos, etc., deberá entenderse que también se podrán utilizar otros ácidos, bases, solventes, agentes condensadores, agentes reductores, agentes desprotectores, agentes hidrolizantes, catalizadores metálicos, etc., conocidos para aquellos imbuidos en la técnica. En forma similar, se podrá ajustar la temperatura de reacción y duración de las reacciones de acuerdo con los requerimientos que surjan durante el proceso. ----------

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Se especifican los siguientes ejemplos para demostrar los procedimientos sintéticos generales para la preparación de compuestos representativos del presente invento. Se proporcionan ejemplos a fin de ilustrar el aspecto especial de la revelación y no limitar el alcance del presente invento. ----------

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EJEMPLOS. ----------

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Síntesis de los materiales de inicio: ----------

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Síntesis del 6-metil-1,2,3-benzotriazin-4(3*H*)-ona. --------

-

Se preparó el compuesto del título siguiendo el procedimiento delineado en *J. Med. Chem.*, (1992), 35(14),

2626-2630. ----------
-

Se prepararon los siguientes análogos de 6-metil-1,2,3-benzotriazin-4(3H)-ona en forma análoga, ----------
-

8-metil-1,2,3-benzotriazin-4(3H)-ona; ----------
-

7-metil-1,2,3-benzotriazin-4(3H)-ona; ----------
-

6-metil-1,2,3-benzotriazin-4(3H)-ona; ----------
-

8-metoxi-1,2,3-benzotriazin-4(3H)-ona; ----------
-

6-metoxi-1,2,3-benzotriazin-4(3H)-ona; ----------
-

8-cloro-1,2,3-benzotriazin-4(3H)-ona; ----------
-

7-cloro-1,2,3-benzotriazin-4(3H)-ona; ----------
-

6-cloro-1,2,3-benzotriazin-4(3H)-ona; ----------
-

5-cloro-1,2,3-benzotriazin-4(3H)-ona; ----------
-

6,7-difluoro-1,2,3-benzotriazin-4(3H)-ona; ----------
-

8-fluoro-1,2,3-benzotriazin-4(3H)-ona; ----------
-

5-fluoro-1,2,3-benzotriazin-4(3H)-ona; ----------
-

6-fluoro-1,2,3-benzotriazin-4(3H)-ona; ----------
-

5-(6-metoxipiridin-3-il)-1,2,3-benzotriazin-4(3H)-ona; ----
-

7-(6-metoxipiridin-3-il)-1,2,3-benzotriazin-4(3H)-ona; y --
-

7-(trifluorometil)-1,2,3-benzotriazin-4(3H)-ona. ----------
-

Síntesis de 5-tert-butil-1H-isoindole-1,3(2H)-diona -------
-

Se preparó el compuesto del título siguiendo el procedimiento delineado en *Chem. Ber.*, (1877), 10, 1163. --
-

Masa (m/z): 204.12(M^+ +1) ----------
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Se prepararon los siguientes análogos de 5-tert-butil-1H-isoindole-1,3(2H)-diona en forma análoga: ----------
-

4-fluoro-1H-isoindole-1,3(2H)-diona; y ----------
-

5-cloro-1H-isoindole-1,3(2H)-diona. ----------
-

Síntesis de (4-bromobencil)(trifenil)bromuro de fosfonio --

-

Se calentó una mezcla de 1-bromo-4-(bromometil)benceno (5g) y trifenilfosfina(5.24 g) en xileno (20 mL) para someter a reflujo durante 18 horas. Se enfrió la mezcla de la reacción, se filtró, se lavó con hexano y se trató al vacío para obtener el compuesto del título (8 g). Masa (m/z):433.9 (M^+ +1) ----------

Se prepararon las siguientes sales de *Wittig* en forma análoga: ----------

-

[(4-bromo-2-tienil)metil]trifenil bromuro de fosfonio; ----

-

[(6-bromopiridin-3-il)metil](tridenil) bromuro de fosfonio;

(4-bromo-2-fluorobencil)(trifenil) bromuro de fosfonio; ---

-

4-tert-butilbencil)(trifenil) bromuro de fosfonio; --------

-

trifenil[4-(trifluorometil)bencil] bromuro de fosfonio; ---

-

bencil(trifenil) bromuro de fosfonio; ----------

-

(4-bromo-3-fluorobencil)(trifenil) bromuro de fosfonio; ---

-

(4-bromo-2-fluorobencil)(trifenil) bromuro de fosfonio; y -

-

(4-cloro-3-fluorobencil)(trifenil) bromuro de fosfonio. ---

-

Síntesis de 4-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il) ácido butanoico. ----------

-

Etapa a: Síntesis de etil 4-(4-oxo-1,2,3-benzotriazin-3(4H)-il)butanoato. ----------

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Se colocó y disolvió en un frasco de fondo redondo seco, 1,2,3-benzotriazin-4(3*H*)-ona (50 g), etil 4-bromobutanoato (86.2 g) y carbonato de potasio (141 g) en dimetilformamida (350 mL) y se calentó a 60-70°C durante 3-4 horas. Después de enfriar a temperatura ambiente, se agregó agua a la mezcla de la reacción y se extrajo con acetato de etilo. La capa orgánica combinada se lavó con agua, solución salina y se secó sobre sulfato sódico anhidro. Se evaporaron los solventes bajo presión reducida y se purificó el producto crudo mediante columna cromatográfica *flash* sobre gel de sílice utilizando 20% de etilacetato en hexano como eluyente para obtener el compuesto del título (68 g). -----

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Estapa b: Síntesis de 4-(4-oxo-1,2,3-benzotriazin-3(4H)-il) ácido butanoico.----------

-

Se agregó a un compuesto de la solución en agitación (40 g), obtenido de la etapa precedente, en un solvente mezcla de tetrahidrofurano/metanol.agua (3:1:1, 400 mL), monohidrato hidróxido de litio (6.43 g) a 0°C bajo

atmósfera de nitrógeno. Se agitó la mezcla de la reacción a 0°C hasta completar la hidrólisis. Se evaporaron los solventes, se diluyeron con agua y se extrajeron con acetato de etilo. Se acidificaron las capas acuosas con solución de sulfato de hidrógeno sódico acuoso saturado y se extrajo con acetato de etilo. Se lavaron las capas combinadas con agua, solución salina y se secaron sobre sulfato sódico anhidro. Se evaporaron los solvente bajo presión reducida para obtener el compuesto del título (28 g). ----------

Se preparó el siguiente análogo de 4-(4-oxo-1,2,3-benzotriazin-3(4H)-il) ácido butanoico en forma análoga: ---

3-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il) ácido propanoico ----

Síntesis de 3-{4-[(4*S*)-4-bencil-2-oxo-1,3-tiazolidin-3-il]-4 -oxobutil}-1,2,3-benzotriazin-4(3*H*)-ona ----------

Etapa a: Síntesis de (2S)-2-amino-3-fenilpropan-1-ol ------

(**Ref:** *J. Org. Chem.* **1993, *58,*** 3568-3571) ----------

Se agregó a una suspensión de borohidruro de sodio (16.5 g) en tetrahidrofurano seco (600 mL), (L)-fenilalanina (30g) a una porción. Se enfrió el frasco a 0°C bajo atmósfera de nitrógeno. Se agregó Solución iodada (46.18 g) en tetrahidrofurano (150 mL) lentamente en gotas durante 40 minutos, dando por resultado evolución vigorosa de H_2.

Después de completar el agregado de iodo, se calentó la mezcla de la reacción sometiéndola a reflujo durante 18 horas y se enfrió a temperatura ambiente. Se templó la mezcla de la reacción con metanol hasta que la misma se volvió clara. Además, se agitó la solución durante 30 minutos a temperatura ambiente. Se removieron los solventes mediante evaporación giratoria para obtener una pasta blanca que se disolvió en 20% de hidróxido de potasio acuoso (450 mL). Se agitó la solución durante 4 horas y luego se agregó diclorometano. Se separaron las capas orgánicas y se extrajo la capa acuosa con diclorometano. Se lavaron las capas orgánicas combinadas con solución salina y se secaron sobre sulfato sódico anhidro. Se evaporaron los solventes bajo presión reducida para obtener 32.5 g de (L)-fenilalaninol como un líquido viscoso. Se utilizó el producto crudo como tal para la próxima etapa. ----------

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Etapa b: Síntesis de (4S)-4-bencil-1,3-tiazolidine-2-tiona.

(**Ref:** *J. Org. Chem.* **1995, *60,*** 6604-6607). ----------

-

Se agregó a una solución del compuesto (32.5 g) obtenida en la etapa a precedente, en hidróxido de potasio acuoso 1N (1 lit), disulfuro de carbono(68 mL, 5.0 equiv.) y se sometió a reflujo la mezcla de la reacción durante 16 horas. Después de enfriar a temperatura ambiente, se extrajo la solución acuosa con diclorometano. Se lavó la capa orgánica con solución salina, se secó sobre sulfato sódico anhidro y se concentró bajo presión reducida. Se purificó el producto

crudo mediante columna cromatográfica *flash* de gel de sílice utilizando 15% de acetato de etilo en hexano para obtener el compuesto del título (22.5 g). ----------

Etapa c: Síntesis de (4S)-4-bencil-1,3-tiazolidin-2-ona. ---

A una solución (4*S*)-4-bencil-1,3-tiazolidine-2-tiona (38 g) en diclorometano (350 mL), enfriada a 0°C se agregó óxido de propileno (12.7 mL) y ácido trifluoroacético (14 mL). Después de agitar la mezcla de la reacción durante 2 horas, se evaporaron los solventes bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 20% de etilacetato en hexano como eluyente para obtener el compuesto del título (0.9 g). Masa (m/z): 194.18 ----------

Etapa d: Síntesis de 3-{4-[(4S)-4-bencil-2-oxo-1,3-tiazolidin-3-il]-4-oxobutil}-1,2,3-benzotriazin-4(3H)-ona. -------

Se agregó a una solución del compuesto (2.1g), obtenida de la etapa c precedente, en diclorometano (25 mL) enfriada a 0°C, 4-dimetilaminopridina (0.334 g) y trietilamina (5.7 mL). Después de agitar la mezcla de la reacción durante 10 minutos, se agregó 1-(3-dimetilaminopropil)-3-clorhidrato de etilcarbodimida (3.9g) y 4-(4-oxo-1,2,3-benzotriacin-3(4*H*)-il) ácido butanoico (3 g) y se agitó la mezcla de la reacción a temperatura ambiente durante 14 horas. Se agregaron diclorometano y agua a la mezcla de la reacción.

Se separó la capa orgánica, se lavó con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que e purificó mediante columna cromatográfica sobre gel de sílice utilizando 25% de etilacetato en hexano como eluyente para obtener el compuesto del título (4.4 g). Masa (m/z): 409.16

Se preparó el siguiente análogo de 3-{4-[(4S)-4-bencil-2-oxo-1,3-tiazolidin-3-il]-4-oxobutil}-1,2,3-benzotriacin-4(3 H)-ona en forma análoga: ----------

3-{3-[(4*S*)-4-bencil-2-oxo-1,3-tiazolidin-3-il]-3-oxopropil}-1,2,3-benzotriacin-4(3*H*)-ona ----------

Ejemplo 1: Síntesis de (2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriacin-3(4H)-il)etil]-5-(4-pirimidin-5-ilfenil) ácido pentanoico (Compuesto No.1). ----------

Etapa a: Síntesis de 5-O-[tert-butil(difenil)silil]-D-arabinofuranosa. ----------

Se colocó D-Arabinosa (200 g) e imidazole (199 g) en un frasco de fondo redondo de triple cuello y se conectó al vacío elevado durante 30 minutos. Se liberó al vacío bajo atmósfera de nitrógeno y dimetilformamida (1.8 L) se agregó a la mezcla anterior a temperatura ambiente seguido de agregado en gotas de *t*-butildifenilclorosilano (443 mL) durante 10 minutos bajo atmósfera de nitrógeno. Se agitó la

mezcla resultante durante 16 horas a la misma temperatura. Se evaporó dimetilformamida bajo presión reducida. Se colocó el residuo en acetato de etilo y se lavó con agua. Se secó la capa orgánica sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo crudo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 80% de acetato de etilo en hexano como eluyente para obtener el compuesto del título (273 g). Masa (m/z): 389.37(M^+ +1) ---

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Etapa b: Síntesis de 5-O-[tert-butil(difenil)silil]-1,2-O-isopropilideno-β-D-arabinofuranosa. ---

-

Se cargó a la solución del compuesto (273 g), obtenida de la etapa anterior, en acetona (2.5 L) ácido DL-canforsulfónico (16 g) y sulfato de cobre anhidro (346 g) bajo una atmósfera de nitrógeno a temperatura ambiente. Se agitó la mezcla de la reacción durante 16 horas a la misma temperatura. Se agregó una solución saturada de bicarbonato de sodio (2 L) en gotas hasta obtener un pH básico, y la mezcla de la reacción se agitó más durante 2 horas a la misma temperatura. Se filtró la mezcla resultante utilizando un embudo *Buchner* y se lavó el residuo con acetona. Se concentró el filtrado, se disolvió en acetato de etilo y se lavó con agua. Se secó la capa orgánica sobre sulfato sódico anhidro, se filtó y se evaporó bajo presión reducida para proporcionar el compuesto del título (295 g). Masa (m/z): 429.41(M^+ +1) ---

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Etapa c: Síntesis de 5-O-[tert-butil(difenil)silil]-1,2-O-isopropilideno-β-D-treo-pentofuranos-3-ulosa ----------

Se colocó cloruro de oxalilo (145 ml) y diclorometano (1 L) en un frasco de fondo redondo de tres cuellos y se enfrió a -75°C bajo atmósfera de nitrógeno. Se agregó dimetil-sulfóxido (212 mL) en gotas a la solución anterior manteniendo la temperatura de reacción a -70°C. Se agitó la mezcla de la reacción durante 30 minutos a la misma temperatura, luego se agregó lentamente una solución del compuesto (285 g) obtenida de la etapa b precedente, en diclorometano (1 L), a la mezcla anterior, manteniendo la temperatura de reacción de -70°C. Después de 20 minutos del agregado anterior, se agregó trietilamina (560 mL) en gotas a la misma temperatura. Luego se agregó solución saturada de cloruro de amoníaco en agua (1.5 L) después de 30 minutos y se permitió elevar la temperatura de reacción a temperatura ambiente. Se extrajo la mezcla de la reacción con diclorometano. Se secaron los extractos orgánicos sobre sulfato sódico anhidro, se filtró y se evaporó bajo presión reducida para obtener el compuesto del título (285 g) -----

Etapa d: Síntesis de 5-O-[tert-butil(difenil)silil]-3-deoxi-3-(2-etoxi-2-oxoetilideno)-1,2-O-isopropilideno-β-D-arabi-nofuranosa ----------

Se cargó a la suspensión de hidruro de sodio (29.4 g, 60% en aceite.) en tetrahidrofurano (1L) a 0°C, fosfonoacetato

de trietilo (200 mL). Después de 20 min, se agregó una solución del compuesto (285 g), obtenida de la etapa c precedente, en tetrahidrofurano (2 L) en gotas y la mezcla de la reacción se agitó durante 1 hora a la misma temperatura. Se agregó una solución saturada de cloruro de amoníaco en agua (1.5 L) a la mezcla de la reacción. Se extrajo la mezcla resultante con acetato de etilo. Se secaron extractos combinados sobre sulfato sódico anhidro y se evaporó bajo presión reducida para producir un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 15% de acetato de etilo en hexano como eluyente para obtener el compuesto del título (275 g). Masa (m/z): 497.43 (M^+ +1) ----------

Etapa e: Síntesis de 5-O-[tert-butil(difenil)silil]-3-deoxi-3-(2-etoxi-2-oxoetil)-1,2-O-isopropilideno-β-D-lixofuranosa y 5-O-[tert-butil(difenil)silil]-3-deoxi-3-(2-etoxi-2-oxoetil)-1,2-O-isopropilideno-α-L-ribofuranosa ----------

Se agregó 10% de paladio sobre carbón (100 g) a la solución del compuesto (275 g), obtenida de la etapa d anterior, en tetrahidrofurano (2 L) y metanol (1 L) a temperatura ambiente y se proporcionó hidrógeno a 50 psi (Aparato Paar) durante 2 horas. Se filtró la mezcla de la reacción a través de un dispositivo de filtración y se lavó el residuo con acetato de etilo. Se concentró el filtrado para obtener una mezcla de 5-O-[tert-butil(difenil)silil]-3-deoxi-3-(2-etoxi-2-oxoetil)-1,2-O-isopropilideno-β-D-lixofuranosa y 5-O-[pert -butil(difenil)silil]-3-deoxi-3-(2-etoxi-2-oxoetil)-1,2-O-isopropilideno-α-L-ribofuranosa (275 g).

Masa (m/z): 499.42 (M^+ +1) ----------

Etapa f: Síntesis de 5-O-[tert-butil(difenil)silil]-3-deoxi-3-(2-hidroxietil)-1,2-O-isopropilideno-β-D-lixofuranosa y 5-O-[tert-butil(difenil)silil]-3-deoxi-3-(2-hidroxietil)-1,2-O -isopropilideno-α-L-ribofuranosa -------

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Se agregó a la suspensión de hidruro de aluminio litio (48 g) en tetrahidrofurano (1 L) una solución del compuesto (275 g), obtenida de la etapa e anterior, en tetrahidrofurano (1.5 L) a -50°C. Se permitió que la mezcla resultante llegara a 0°C. Se agitó la mezcla de la reacción durante 30 minutos a la misma temperatura y nuevamene se enfrió a -50°C. Se agregó lentamene acetato de etilo (2 L) mientras se mantenía a -50°C. Se agregó una solución acuosa de cloruro de amoníaco (100 g) en agua (2.5 L) a la misma temperatura. Se permitió lentamente que la mezcla de la reacción se calentara a temperatura ambiente y se agitó la mezcla de la reacción durante 12 horas a la misma temperatura. Luego se filtró la mezcla de la reacción a través de un dispositivo de filtración y el residuo se lavó con acetato de etilo. Se secó la capa orgánica sobre sulfato sódico anhidro, se filtró, se concentró bajo presión reducida y el residuo así obtenido se purificó mediante columna cromatográfica sobre gel de sílice utilizando 50% de acetato de etilo en hexano como eluyente para obtener el 5-O-[tert-butil (difenil) silil]-3-deoxi-3-(2-hidroxietil)-1,2-O-isopropilideno-β-D-lixofuranosa (130 g) y 5-O-[tert-butil(difenil)silil]-3-deoxi-3-(2-

hidroxietil)-1,2-O-isopropilideno-α-L-ribofurano-sa (40.0 g). Masa (m/z): 457.39(M^+ +1). ----------

Etapa g: Síntesis de 5-O-[tert-butil(difenil)silil]-3-deoxi-1,2-O-isopropilideno-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-β-D-lixofuranosa ----------

Se secaron 5-O-[tert-butil(difenil)silil]-3-deoxi-3-(2-hidroxietil)-1,2 -O-isopropilideno-β-D-lixofuranoss (35g), trifenilfosfina (30.8g) y 1,2,3-benzotriazin-4(3*H*)-ona (12.6g) al vacío elevado en un frasco de fondo redondo durante 10 minutos. Luego se liberó el vacío bajo una atmósfera de nitrógeno y se agregó tetrahidrofurano (70mL) a la mezcla de la reacción precedente. Se enfrió la mezcla de la reacción a 0°C y se agregó lentamente diisopropil azodicarboxilato (17mL). Se agitó la mezcla de la reacción durante 30 minutos a la misma temperatura, y luego se templó con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua, solución salina, se secó sobre sulfato sódico anhidro y se concentró para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 30% de acetato de etilo en hexano como eluyente para obtener el compuesto del título (50g). Masa (m/z):586.05 (M^+ +1) ----------

Etapa h: Síntesis de 3-deoxi-1,2-O-isopropilideno-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-β-D-lixofuranosa ----

Se agregó a una solución del compuesto (50g), obtenida de la etapa g anterior, en tetrahidrofurano seco (400mL) a 0°C, fluoruro de amoníaco tetra-butilo (170mL). Se agitó inicialmente la mezcla resultante a 0°C durante 1 hora, y luego a temperatura ambiente durante 4 horas. Se enfrió la mezcla de la reacción a 0°C, se templó con cloruro de amoníaco saturado y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina, se secó sobre sulfato sódico anhidro y se concentró. El residuo así obtenido se purificó mediante columna cromatográfica sobre gel de sílice utilizando 80% de acetato de etilo en hexano como eluyente para proporcionar el compuesto del título (22 g). ----------

Masa (m/z):369.98 (M^+ +23) ----------

Etapa i: Síntesis de (5S)-3-deoxi-4,5-O-isopropilideno-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-D-arabino-pento-dialdo-5,2-furanosa ----------

Se colocó cloruro de oxalilo (13.7mL) y diclorometano (300mL) en un frasco de fondo redondo de tres cuellos y se enfrió a -78°C. Se agregó dimetilsulfóxido (20.2mL) en gotas a la mezcla de la reacción. Se calentó la mezcla de la reacción a -35°C durante 5 a 10 minutos y nuevamente se enfrió a -78°C. Se agregó lentamente a una solución del compuesto (22 g), obtenida de la etapa h anterior, en diclorometano (200mL) mientras se mantenía la misma

temperatura. Se agitó la mezcla de la reacción durante 45 minutos hasta que la temperatura de reacción llegó a -35°C. Se enfrió nuevamente la mezcla de la reacción a -78°C y se agregó trietilamina (53mL). Se agitó la mezcla de la reacción durante 30 minutos adicionales, y se permitió que la temperatura llegara a -35°C. Se templó la mezcla de la reacción con solución de cloruro de amoníaco saturada y se extrajo con diclorometano. Se lavaron las capas orgánicas combinadas con agua y solución salina, se secaron sobre sulfato sódico anhidro y se concentraron para proporcionar el compuesto del título (22g). ----------

Etapa j: Síntesis de 3-(2-{(3aS,5R,6S,6aS)-5-[(E)-2-(4-bromofenil)vinil]-2,2-dimetiltetrahidrofuro[2,3-d][1,3]dioxol-6-il}etil)-1,2,3-benzotriazin-4(3H)-ona ----------

Se agregó a la suspensión de hidruro de sodio (3.3g, 60% en aceite) en tetrahidrofurano (50mL) enfriada a 0°C, (4-bromobencil) bromuro de trifenilfosfonio (48.8g) en tetrahidrofurano (100mL). Se agregó a una solución del compuesto (22g), obtenida de la etapa i anterior, en tetrahidrofurano (100mL) en gotas después de 20 minutos, y se agitó la mezcla de la reacción durante 1 hora a la misma temperatura. Se templó la mezcla de la reacción con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida y el residuo así obtenido se purificó mediante columna

cromatográfica utilizando 30% de acetato de etilo en hexano como eluyente para proporcionar el compuesto del título (24.5g). Masa (m/z):498.84 (M^+ +1) ----------

Etapa k: Síntesis de 3-(2-{(3aS,5R,6S,6aS)-2,2-dimetil - 5 -[(E)-2-(4-pirimidin-5-ilfenil)vinil]tetrahidrofuro [2,3-d] [1,3] dioxol-6-il}etil)-1,2,3-benzotriazin-4(3H)-ona ----------

Se secó una mezcla del compuesto (0.35g), obtenida de la etapa j anterior, pirimidin-5-ácido ilborónico (0.174g), tetraquistrifenilfosfinopaladio (0) (0.081g) y carbonato de potasio (0.291g) al vacío elevado durante 10 minutos y se agregó dimetilformamida seca (5mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 120°C durante 2 horas, y luego se templó con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 40% de acetato de etilo en hexano como eluyente para proporcinar el compuesto del título (0.3g). Masa (m/z): 498.0(M^+ +1) ----------

Etapa l: Síntesis de 3-(2-{(3aS,5R,6S,6aS)-2,2-dimetil-5-[2-(4-pirimidin-5-ilfenil)etil]tetrahidrofuro[2,3-d] [1,3] dio-xol-6-il}etil)-1,2,3-benzotriazin-4(3H)-ona ----------

Se agregó a la solución del compuesto (0.3g), obtenida de la etapa k anterior, en una mezcla de solvente de tetrahidrofurano:metanol (10mL, 1:1) 10% de paladio sobre carbón (0.15g) a temperatura ambiente y se hidrogenó la mezcla de la reacción con hidrógeno a la presión de 35 psi durante 4 horas en un aparato *Paar*. Se filtró la mezcla de la reacción a través de un dispositivo de filtración y se lavó el residuo con metanol. Se concentró el filtrado para producir el compuesto del título (0.3g). ----------

Etapa m: Síntesis de 3-(2-{(2R,3R,4S,5R)-4,5-dihidroxi-2-[2-(4-pirimidin-5-ilfenil)etil]tetrahidrofuran-3-il}etil)-1,2,3 -benzotriazin-4(3H)-ona ----------

Se agregó ácido perclórico (0.2mL) a una solución del compuesto (0.3g), obtenida de la etapa 1 anterior, en acetonitrilo (4mL) y agua (0.2mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 55°C durante 30 minutos. Luego se templó la mezcla de la reacción utilizando solución de bicarbonato de sodio. Se evaporaron los solventes bajo presión reducida. Se colocó el residuo así obtenido en acetato de etilo y agua. Se separó la capa orgánica y se lavó con agua y solución salina y se secó sobre sulfato sódico anhidro. Se concentró el solvente bajo presión reducida para producir el compuesto del título (0.25g). ----

Etapa n: Síntesis de (2S,3R)-3-(formiloxi)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-(4-pirimidin-5-ilfenil)

ácido pentanoico ----------

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Se agregó a una solución del compuesto (0.25g), obtenido de la etapa m anterior, en *tert*-butanol:tetrahidrofurano (5mL:5mL) a 0°C, una solución de metaperiodato de sodio (0.465 g en 5 mL de agua). Se agitó la mezcla de la reacción durante 2 horas a la misma temperatura y se agregó permangnato de potasio (0.017g) a 0°C. Después de agitar la mezcla de la reacción durante 6 horas adicionales a temperatura ambiente, se evaporó la mezcla de la reacción en un evaporador giratorio. Se colocó el residuo en agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener el compuesto del título (0.25g). ----------

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Etapa o: Síntesis de (2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-(4-pirimidin-5-ilfenil) ácido pentanoico ----------

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Se agregó carbonato de potasio (0.081g) a una solución del compuesto (0.25g), obtenida de la etapa n precedente, en metanol (5mL) y tetrahidrofurano (5mL) at 0°C. Se agitó la mezcla de la reacción a temperatura ambiente durante 3 horas. Se evaporaron los solventes y se colocó el residuo en agua y acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para

obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 60% de acetato de etilo en hexano como eluyente para obtener el compuesto del título (0.030g). Masa (m/z):446.0 (M^+ +1). ----------

^{1}HNMR (CD_3OD): δ 9.09 (s, 1H), 9.03 (s, 1H), 8.30 (d, 1H, J = 8Hz), 8.14 (d, 1H, J = 8Hz), 8.05- 8.03 (m, 1H), 7.89-7.87 (m, 1H), 7.61 (d, 2H, J = 8Hz), 7.53- 7.59 (m,1H), 7.35 (d, 2H, J = 8Hz), 4.57- 4.52 (m, 2H), 3.79-3.77 (m, 1H), 2.89 -2.87 (m, 1H), 2.69 - 2.67 (m, 1H), 2.47- 2.46 (m, 1H), 2.29- 2.25 (m, 2H), 1.82- 1.77 (m, 2H). ----------

Ejemplo 1A: Síntesis de (2S,3R)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 86). ----------

Etapa a: Síntesis de 3-(2-{(3a*S*,5*R*,6*S*,6a*S*)-5-[(*E*)-2-(4-bromofenil)etenil]-2,2-dimetiltetrahidrofuro[2,3-*d*][1,3]dio-xol-6-il}etil)-1,2,3-benzotriazin-4(3*H*)-ona ----------

Se agregó a la suspension de t-butóxido de potasio (3.3g, 60% en aceite) en sulfóxido de dimetilo (50mL) enfriada a 0°C, 4-bromobencil bromuro de trifenil-fosfonio (48.8g) en sulfóxido de dimetilo (100mL). Después de 20 minutos, se agregó al compuesto (22g) obtenido de la etapa i del ejemplo I anterior, en sulfóxido de dimetilo (100mL) en gotas y se agitó la mezcla de la reacción durante 1 hora a la misma temperatura. Se templó la reacción con agua y se

extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida. Se realizó la purificación sobre columna de gel de sílice utilizando 30% de acetato de etilo como eluyente para obtener el compuesto del título (24.5g). ----------

Etapa b: Síntesis de 3-{2-[(3a*S*,5*R*,6*S*,6a*S*)-5-{(*E*)-2-[4-(6-metoxipiridin-3-il)fenil]etenil}-2,2-dimetiltetrahidrofuro[2,3-*d*][1,3]dioxol-6-il]etil}-1,2,3-benzotriazin-4(3*H*)-ona.

Se secó una mezcla del compuesto (12gms), obtenida de la etapa a precedente, 2-metoxi-5-piridina ácido borónico (7.4gms), tetraquistrifenilfosfinopaladio (0) (2.8gms) y carbonato de potasio (10gms) al vacío elevado durante 10 minutos y se agregó dimetilformamida seca (60ml) a temperatura ambiente. Se calentó la mezcla de la reacción a 120°C durante 2 horas, y luego se templó con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 40% de acetato de etilo en hexano como eluyente para producir el compuesto del título (8.5gms). ----------

Etapa c: Síntesis de 3-{2-[(3a*S*,5*R*,6*S*,6a*S*)-5-{2-[4-(6-metoxipiridin-3-il)fenil]etil}-2,2-

dimetiltetrahidrofuro[2,3 -*d*][1,3]dioxol-6-il]etil}-1,2,3-benzotriazin-4(3*H*)-ona -----

Se agregó a la solución del compuesto (8.5g), obtenido de la etapa b precedente, en una mezcla de solvente de tetrahidrofurano:metanol (60mL:40mL), 10% de paladio sobre carbón (4g) a temperatura ambiente y se hidrogenó la mezcla de la reacción con hidrógeno a la presión de 35 psi durante 4 horas en un aparato *Paar*. Se filtró la mezcla de la reacción a través de un dispositivo de filtración y se lavó el residuo con metanol. Se concentró el filtrado para producir el compuesto del título (8.1g). ----------

Etapa d: Síntesis de 3-{2-[(2*R*,3*R*,4*S*,5*R*)-4,5-dihidroxi-2-{2-[4-(6-metoxipiridin-3-il) fenil] etil} tetrahidrofuran-3-il] etil}-1,2,3-benzotriazin-4(3*H*)-ona ----------

Se agregó ácido perclórico (4.8ml) a una solución del compuesto (8.1gms), obtenida de la etapa c precedente, en acetonitrilo (50ml) y agua (8ml) a temperatura ambiente. Se calentó la mezcla de la reacción a 55°C durante 30 minutos. Luego se templó la mezcla de la reacción utilizando solución de bicarbonato de sodio. Se evaporaron los solventes bajo presión reducida. El residuo así obtenido se colocó en acetato de etilo y agua. Se separó la capa orgánica y se lavó con agua y solución salina y se secó sobre sulfato sódico anhidro. Se concentró el solvente sobre presión reducida para producir el compuesto del título (8gm). ------

Etapa e: Síntesis de (2*S*,3*R*)-3-(formiloxi)-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4*H*)-il)etil]ácido pentanoico. ----------

Se agregó a una solución del compuesto (8g), obtenido de la etapa d precedente, en *tert*-butanol:tetrahidrofurano (40mL:40mL) a 0°C, una solución de metaperiodato de sodio (14g en 40 mL de agua). Se agitó la mezcla de la reacción durante 2 horas a la misma temperatura y se agregó permangnato de potasio (518mg) a 0°C. Después de agitar la mezcla de la reacción durante 6 horas adicionales, a temperatura ambiente, se evaporó la mezcla de la reacción sobre evaporador giratorio. Se colocó el residuo en agua y acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener el compuesto del título (8g). ----------

Etapa f: Síntesis de (2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin -3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4*H*) -il)etil] ácido pentanoico ----------

Se agregó carbonato de potasio (2.3g) a una solución del compuesto (8g), obtenida de la etapa e anterior, en metanol (40mL) y tetrahidrofurano (30mL) a 0°C. Se agitó la mezcla de la reacción a temperatura ambiente durante 3 horas. Se evaporaron los solventes y se colocó el residuo en agua y acetato de etilo. Se lavó la capa orgánica con agua y

solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 60% de acetato de etilo en hexano como eluyente para obtener el compuesto del tìtulo (3g). **Masa (m/z):** 474.87(M^+ +1); **^{1}H NMR (400 MHz, MeOD):** δ 8.32- 8.30 (2H, m), 8.16- 8.14 (1H, m), 8.04- 8.03 (1H, m), 7.92- 7.88 (2H, m), 7.46 (2H, d, J= 8Hz), 7.24 (2H, m, J= 8Hz), 6.86 (1H, d, J= 8Hz), 4.57- 4.53 (2H, m), 3.93 (3H, s), 3.78-3.83 (1H, m), 2.83- 2.80 (1H, m), 2.63- 2.60 (1H, m), 2.52- 2.49 (1H, m), 2.32- 2.28 (2H, m), 1.80- 1.76 (2H, m). ----------

Ejemplo 1B: Síntesis de (2*S*,3*R*)-3-hidroxi-5-[4-(6-hidroxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 226). ------

Se agregó a una solución del compuesto (0.2 gm), obtenida del Ejemplo 1A anterior en tolueno seco (5ml), se enfrió a -78°C, se agregó tribromuro de boron (0.5 ml) y se agitó el contenido a temperatura ambiente durante 4 horas. Se agregó acetato de etilo y agua a la mezcla de la reacción. Se separó la capa orgánica, se lavó con agua y solución salina y se secó sobre sulfado sódico anhidro. Se evaporó el solvente para obtener un residuo que se purificó mediante cromatografía de capa delgada preparatoria (2 mm de espesor) utilizando 15% de metanol en diclorometano como eluyente para obtener el compuesto del título (60mg). **Masa (m/z):** 461.23 (M^+ +1); **^{1}HNMR (CD_3OD):** 8.30 (d, 1H, J =

8Hz), 8.15 (d, 1H, J = 8Hz), 8.06-8.01 (m, 2H), 7.88 (t, 1H, J = 8Hz), 7.79-7.76 (m, 1H), 7.43 (d, 2H, J = 12Hz), 7.25 (d, 2H, J = 12Hz), 6.75 (d, 1H, J = 12Hz), 4.58- 4.51 (m, 2H), 3.82-3.76 (m, 1H), 2.88 -2.78 (m, 1H), 2.66 - 2.57 (m, 1H), 2.54- 2.47 (m, 1H), 2.33- 2.25 (m, 2H), 1.84- 1.70 (m, 2H). ----------

Ejemplo 1C: Síntesis de (2*S*,3*R*)-3-(acetiloxi)-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4 *H*)-il)etil]ácido pentanoico (Compuesto Nro. 229). -----

Se agregó azodicarboxilato diisopropilo (63 mg) a una solución del compuesto (100 mg) obtenida del Ejemplo 1A precedente, tri-n-butilfosfina (93 mg), ácido acético (1 ml) en tetrahidrofurano seco (3 ml) a 0°C. Se agitó la mezcla de la reacción durante 1 hora y se concentró. Se colocó el residuo en acetato de etilo y se lavó con agua y solución salina. Se concentró la capa orgánica para obtener un residuo aceitoso que se purificó sobre cromatografía de capa delgada preparativa (2 mm de espesor) utilizando 10% de metanol en diclorometano para obtener el compuesto del título (80 mg) (formado probablemente mediante esterificación de ácido acético (utilizado en gran exceso) y no debido a la reacción de *Mitsunobu*). **Masa (m/z):** 517.06 (M^+ +1); **^{1}HNMR:** δ 8.37 (m, 2H), 8.15 (d, 1H, J = 8Hz), 7.97- 7.93 (m, 1H), 7.82- 7.80 (m, 1H), 7.41(d, 2H, J = 8Hz), 7.20 (d, 2H, J = 8Hz), 6.83 (d, 1H, J = 8Hz), 5.28- 5.27 (m, 1H), 4.56- 4.58 (m, 2H), 4.01 (s, 3H), 2.85- 2.80 (m, 1H), 2.55- 2.75 (m, 2H), 2.31- 2.29 (m, 2H), 2.25- 2.10

(m, 2H), 2.063 (s, 3H). ----------

Ejemplo 1D: Síntesis de (2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il) fenil]ácido pentanoico (Compuesto Nro.88). ----------

Etapa a: Síntesis de 5-*O*-[*tert*-butil(difenil)silil]-3-deoxi-3-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-1,2-*O*-(1-metiletilideno) -β -D-lixofuranosa ----------

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Se secó 5-O-[tert-butil(difenil)silil]-3-deoxi-3-(2-hidroxi-etil)-1,2 -O-isopropilideno-β-D-lixofuranosa (14g), trife-nilfosfina (12g) y ftalimida (5g) al vacío elevado en un frasco de fondo redondo durante 10 minutos. Luego se liberó el vacío bajo atmósfera de nitrógeno y se agregó tetrahidrofurano (100mL) a la mezcla de la reacción anterior. Se enfrió la mezcla de la reacción a 0°C y se agregó azodicarboxilato dietilo (7.8mL) lentamente. Se agitó la mezcla de la reacción durante 30 minutos a la misma temperatura, y luego se templó con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua, solución salina, se secó sobre sulfato sódico anhidro y se concentró para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 30% de acetato de etilo en hexano como eluyente para obtener el compuesto del título (11g). ----------

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Etapa b: Síntesis de 3-deoxi-3-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-1,2-*O*-(1-metiletilideno)- β-D-lixofura-nosa ----------

Se agregó a una solución del compuesto (11g), obtenida de la etapa a anterior, en tetrahidrofurano seco, (50mL) a 0°C, fluoruro de amoníaco tetra-butilo (41.36mL). La mezcla resultante se agitó inicialmente a 0°C durante 1 hora, y luego a temperatura ambiente durante 4 horas. Se enfrió la mezcla de la reacción a 0°C, se templó con cloruro de amoníaco saturado y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina, se secó sobre sulfato sódico anhidro y se concentró. Se purificó el residuo así obtenido mediante columna cromatográfica sobre gel de sílice utilizando 80% de acetato de etilo en hexano como eluyente para obtener el compuesto del título (5 g). --

Etapa c: Síntesis de (5*S*)-3-deoxi-3-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-4,5-*O*-(1-metiletilideno)- D-*arabino*-pentodialdo-5,2-furanosa ----------

Se colocó cloruro de oxalilo (4.5mL) y diclorometano (20mL) en un frasco de fondo redondo de tres cuellos y se enfrió a -78°C. Se agregó dimetilsulfóxido (6.6mL) en gotas a la mezcla de la reacción. Se calentó la misma a -35°C durante 5 a 10 minutos y se enfrió nuevamente a -78°C. Se agregó una solución del compuesto (7.2 g), obtenida de la etapa b anterior, en diclorometano (20mL) lentamente mientras se

mantenía la misma temperatura. Se agitó la mezcla de la reacción durante 45 minutos hasta que la temperatura de la reacción llegó a -35°C. Se enfrió nuevamente la mezcla de la reacción a -78°C y se agregó trietilamina (17.3mL). Se agitó la mezcla de la reacción durante 30 minutos adicionales, y se permitió que la temperatura llegara a -35°C. Se templó la mezcla de la reacción con solución de cloruro de amoníaco saturada y se extrajo con diclorometano. Se lavaron las capas orgánicas combinadas con agua y solución salina, se secaron sobre sulfato sódico anhidro y se concentraron para proporcionar el compuesto del título (7.3g). ----------

Etapa d: Síntesis de 2-(2-{(3a*S*,5*R*,6*S*,6a*S*)-5-[(*E*)-2-(4-bromofenil)etenil]-2,2-dimetiltetrahidrofuro[2,3-*d*][1,3]dio-xol-6-il}etil)-1*H*-isoindole-1,3(2*H*)-diona ----------

Se agregó a la suspensión de t-butóxido de potasio (2.3g) en sulfóxido de dimetilo (30ml) enfriada a 0^0 C, (4-bromobencil) bromuro de trifenilfosfonio (12.2gm) en sulfóxido de dimetilo (20ml). Después de 20 minutos, se agregó una solución del compuesto (4.1gms) obtenida de la etapa c anterior, en sulfóxido de dimetilo (10ml) en gotas y se agitó la mezcla de la reacción durante 1 hora a la misma temperatura. Se templó la mezcla de la reacción con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida. Se realizó la purificación sobre columna de gel

de sílice utilizando 40% de acetato de etilo en hexano como eluyente para proporcionar el compuesto del título (4gms).

Etapa e: Síntesis de 2-{2-[(3a*S*,5*R*,6*S*,6a*S*)-5-{(*E*)-2-[4-(6-metoxipiridin-3-il)fenil] etenil} -2,2-dimetiltetrahidrofuro [2,3-*d*][1,3]dioxol-6-il]etil}-1*H*-isoindole-1,3(2*H*)-diona. --

Se secó una mezcla del compuesto (1g), obtenida de la etapa d anterior, 2-metoxi-5-piridina ácido borónico (0.614g), tetraquistrifenilfosfinopaladio (0) (0.115g) y carbonato de potasio (0.832g) al vacío elevado durante 10 minutos y se agregó dimetilformamida seca (8mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 120°C durante 2 horas, y luego se templó con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 30% de acetato de etilo en hexano como eluyente para proporcionar el compuesto del título (0.62g).

Etapa f: Síntesis de 2-{2-[(3a*S*,5*R*,6*S*,6a*S*)-5-{2-[4-(6-metoxipiridin-3-il)fenil]etil}-2,2-dimetiltetrahidrofuro[2,3 -*d*][1,3]dioxol-6-il]etil}-1*H*-isoindole-1,3(2*H*)-diona. ------

Se agregó a la solución del compuesto (0.6g), obtenida de la etapa e precedente, en metanol (10mL), 10% de paladio sobre carbón (0.05g) a temperatura ambiente y se hidrogenó

la mezcla de la reacción con hidrógeno a la presión de 35 psi durante 4 horas en un aparato *Paar*. Se filtró la mezcla de la reacción a través de un dispositivo de filtración y se lavó el residuo con metanol. El filtrado se concentró para producir el compuesto del título (0.56g). ----------

Etapa g: Síntesis de 2-{2-[(2*R*,3*R*,4*S*,5*R*)-4,5-dihidroxi-2-{2-[4-(6-metoxipiridin-3-il)fenil] etil} tetrahidrofuran-3-il] etil}-1*H*-isoindole-1,3(2*H*)-diona ----------

Se agregó ácido perclórico (0.4mL) a una solución del compuesto (0.5g), obtenida de la etapa f precedente, en acetonitrilo (4mL) y agua (0.8mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 55°C durante 30 minutos. Luego se templó la mezcla de la reacción utilizando solución de bicarbonato de sodio. Se evaporaron los solventes bajo presión reducida. El residuo así obtenido se colocó en acetato de etilo y agua. Se separó la capa orgánica y se lavó con agua y solución salina y se secó sobre sulfato sódico anhidro. Se concentró el solvente bajo presión reducida para producir el compuesto del título (0.51g). ----

Etapa h: Síntesis de (1*R*,2*S*)-4-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-2-formil-1-{2-[4-(6-metoxipiridin-3-il)fenil] etil}formato de butilo ----------

Se agregó a una solución del compuesto (0.56g), obtenida de la etapa g precedente, en metanol (4mL) a 0°C, una solución

de metaperiodato de sodio (0.736 g en 1 mL de agua). Se agitó la mezcla de la reacción durante 2 horas a la misma temperatura. Después de agitar la mezcla de la reacción durante 1 hora adicional a temperatura ambiente, se evaporó la mezcla de la reacción en un evaporador giratorio. Se colocó el residuo en agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener el compuesto del título (0.54g). ----------

Etapa i: Síntesis de (2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-(formiloxi)-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico. ----------

Se colocó el compuesto (0.54 g) obtenido en acetonitrilo (6mL) y agua (1mL). A esta solución se agregó fosfato de sodiodihidrógeno (0.054g). Se enfrió la mezcla de la reacción a 0°C y se agregó peróxido de hidrógeno (1mL) y clorito de sodio (0.208 g). Después de agitar 1 hora adicional la mezcla de la reacción, se evaporaron los solventes en evaporador giratorio; se colocó el residuo en agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida, para obtener el compuesto del título (0.5 g). ---

Etapa j: Síntesis de (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)fe-nil]ácido pentanoico ----------

Se agregó carbonato de potasio (0.165g) a una solución del compuesto (0.4g), obtenida de la etapa i anterior, en metanol (6mL) a 0°C. Se agitó la mezcla de la reacción a temperatura ambiente durante 3 horas. Se evaporaron los solventes y se colocó el residuo en agua y acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó con TLC preparatorio utilizando 7% de metanol en etilacetato como eluyente para obtener el compuesto del título (0.13gm). **Masa (m/z):** 474.88(M^+ +1); **^{1}HNMR ($CDCl_3$):-** δ 8.35 (s, 1H), 7.83-7.81 (m, 2H), 7.77-7.69 (m, 3H), 7.42 (d, 2H, J = 3Hz), 7.25 (d, 2H, J = 6Hz), 6.80 (d, 1H, J = 6Hz), 3.97 (s, 3H), 3.87-3.78 (m, 3H), 2.89(m, 1H), 2.69 (m, 1H), 2.57(m, 1H), 2.15-1.98 (m, 2H), 1.84-1.79 (m, 2H); ----

Ejemplo 1E: Síntesis de (2S,3R)-5-(2',4'-difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hi-droxi ácido pentanoico (Compuesto Nro. 97). ----------

Etapa a: Síntesis de 2-(2-{(3a*S*,5*R*,6*S*,6a*S*)-5-[(*E*)-2-(3',5'-difluorobifenil-4-il)etenil]-2,2-dimetiltetrahidrofuro [2,3-*d*] [1,3]dioxol-6-il}etil)-1*H*-isoindole-1,3(2*H*)-diona --------

Se secó una mezcla del compuesto (0.2g), obtenido de la etapa d del Ejemplo 1D anterior, 3,5-difluorofenil ácido borónico (0.135g), tetraquistrifenilfosfinopaladio (0) (0.023g) y carbonato de potasio (0. 2g) al vacío elevado durante 10 minutos y se agregó dimetilformamida seca (3mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 120°C durante 2 horas, y luego se templó con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 30% acetato de etilo en hexano como eluyente para conseguir el compuesto del título (0.205g). ----------

Etapa b: Síntesis de 2-(2-{(3a*S*,5*R*,6*S*,6a*S*)-5-[2-(3',5'-difluorobifenil-4-il)etil]-2,2-dimetiltetrahidrofuro [2,3-*d*] [1,3]dioxol-6-il}etil)-1*H*-isoindole-1,3(2*H*)-diona ----------

Se agregó a la solución del compuesto (0.2g), obtenida de la etapa a anterior, en tetrahidrofurano (10mL), 10% de paladio sobre carbón (0.1g) a temperatura ambiente y se hidrogenó la mezcla de la reacción con hidrógeno a la presión de 35 psi durante 4 horas en un aparato *Paar*. Se filtró la mezcla de la reacción a través de un dispositivo de filtración y se lavó el residuo con metanol. Se concentró el filtrado para proporcionar el compuesto del título (0.2g). ----------

Etapa c: Síntesis de 2-(2-{(2*R*,3*R*,4*S*,5*R*)-2-[2-(3',5'-difluorobifenil-4-il)etil]-4,5- dihidroxitetrahidrofuran -3-il}etil)-1*H*-isoindole-1,3(2*H*)-diona ----------

Se agregó ácido perclórico (0.3mL) a una solución del compuesto (0.2g), obtenida de la etapa b anterior, en acetonitrilo (6mL) y agua (2mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 55°C durante 30 minutos. Luego se templó la mezcla de la reacción utilizando solución de bicarbonato de sodio. Se evaporaron los solventes bajo presión reducida. Se colocó el residuo así obtenido en acetato de etilo y agua. Se separó la capa orgánica y se lavó con agua y solución salina y se secó sobre sulfato sódico anhidro. Se concentró el solvente bajo presión reducida para producir el compuesto del título (0.15g). ----

Etapa d: Síntesis de (1*R*,2*S*)-1-[2-(3',5'-difluorobifenil-4-il)etil]-4-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-2-forma-to formilbutilo ----------

Se agregó a una solución del compuesto (0.15g), obtenido de la etapa c precedente, en metanol (6mL) a 0°C, una solución de metaperiodato de sodio (0.15 g en 1 mL de agua). Se agitó la mezcla de la reacción durante 2 horas a la misma temperatura. Después de agitar la mezcla de la reacción durante 1 hora adicional a temperatura ambiente, se evaporó la mezcla de la reacción sobre el evaporador giratorio. Se colocó el residuo en agua y se extrajo con acetato de

etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener el compuesto del título (012g). ----------

Etapa e: Síntesis de (2*S*,3*R*)-5-(3',5'-difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-(formi-loxi)ácido pentanoico ----------

Se agregó el compuesto (0.12 g) obtenido de la etapa d, se colocó en acetonitrilo (6mL) y agua (1mL), se agregó a esta solución fosfato de sodiodihidrógeno (0.05g). Se enfrió la mezcla de la reacción a 0°C y se agregó peróxido de sodio (0.5mL) y clorito de sodio (0.15 g). Después de agitar la mezcla de la reacción durante 1 hora adicional, se evaporaron los solventes sobre evaporador giratorio, se colocó el residuo en agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para conseguir el compuesto del título (0.12 g). ----------

Etapa f: Síntesis de (2*S*,3*R*)-5-(3',5'-difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidro-xi ácido pentanoico ----------

Se agregó carbonato de potasio (0.06g) a una solución del compuesto (0.12g), obtenida de la etapa e anterior, en

metanol (10mL) a 0°C. Se agitó la mezcla de la reacción a temperatura ambiente durante 3 horas. Se evaporaron los solventes y se colocó el residuo en agua y acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó con cromatografía de capa delgada preparatoria utilizando 10% de metanol en etilacetato como eluyente para obtener el compuesto del título (0.025gm). **Masa (m/z):** 480.13(M^+ +1); **^{1}HNMR (CD_3OD):** δ 7.48-7.76 (m, 4H), 7.47-7.37 (m, 3H), 7.25-7.23 (d, 2H), 7.03-6.98 (m, 2H), 3.78-3.72 (m, 3H), 2.85-2.81 (m 1H), 2.65-2.63 (m, 1H), 2.422.40 (m, 1H), 2.10-2.05 (m, 2H), 1.79-1.75 (m, 2H); ----------

Ejemplo 2: Síntesis de (2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-fenil ácido pentanoico (Compuesto Nro. 82). ----------

Etapa a: Síntesis de 3-{2-[(3aS,5R,6S,6aS)-2,2-dimetil-5-(2-feniletil)tetrahidrofuro[2,3-d][1,3]dioxol-6-il]etil}-1,2,3-benzotriazin-4(3H)-ona ----------

Se agregó a la solución del compuesto (0.3g), obtenida de la etapa j del Ejemplo 1, en un solvente, mezcla de tetrahidrofurano:metanol (10mL:10 mL) paladio/carbono (0.2 g, 10%) a temperatura ambiente y se hidrogenó la mezcla de la reacción a la presión de 35 psi durante 4 horas en un aparato *Paar*. Se filtró la mezcla de la reacción a través

de un dispositivo de filtración y el residuo se lavó con metanol. Se concentró el filtrado para producir el compuesto del título (0.3 g). Masa (m/z):421 (M^+). ----------

Etapa b: Síntesis de 3-{2-[(2R,3R,4S,5R)-4,5-dihidroxi-2-(2-fenileti)tetrahidrofuran-3-il]etil}-1,2,3-benzotriazin-4(3H) -ona ----------

Se agregó ácido perclórico (0.2 mL) a una solución del compuesto (0.3g), obtenida de la etapa a anterior, en acetonitrilo (4 mL) y agua (0.3 mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 55°C durante 30 minutos. Luego se templó la misma utilizando una solución de bicarbonato de sodio. Se evaporaron los solventes a presión reducida. El residuo así obtenido se colocó en acetato de etilo y agua. Se separó la capa orgánica y se lavó con agua y solución salina y se secó sobre sulfato sódico anhidro. Se concentró el solvente bajo presión reducida para producir el compuesto del título (0.3 g). ----------

Etapa c: Síntesis de (2S,3R)-3-(formiloxi)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-fenil ácido pentanoico -

Se agregó a una solución del compuesto (0.3 g), obtenida de la etapa b anterior, en *tert*-butanol:tetrahidrofurano (3mL:3mL) a 0°C, una solución de metaperiodato de sodio (0.673 g en 3mL de agua). Se agitó la mezcla de la reacción durante 2 horas a la misma temperatura y se agregó

permangnato de potasio (0.025 g) a 0°C. Después de agitar la mezcla de la reacción durante 6 horas adicionales a temperatura ambiente, se evaporó la misma, se colocó el residuo en agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida, para proporcionar el compuesto del título (0.3 g).

Etapa d: Síntesis de (2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-fenil ácido pentanoico ------

Se agregó carbonato de potasio (0.11 g) a una solución del compuesto (0.3 g), obtenida de la etapa c anterior, en metanol (4mL) y tetrahidrofurano (4mL) a 0°C. Se agitó la mezcla de la reacción a temperatura ambiente durante 3 horas. Se evaporaron los solventes y se colocó el residuo en agua y acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 10% de metanol en diclorometano como eluyente para conseguir el compuesto del título (0.020g). Masa (m/z):368.0 (M^+ +1); ^{1}HNMR (CD_3OD): δ 8.31 (d, 1H, J = 8Hz), 8.15 (d, 1H, J = 8Hz), 8.06- 8.02 (m, 1H), 7.91- 7.89 (m, 2H), 7.62 (d, 2H, J = 8Hz), 7.36 (d, 1H, J = 8Hz), 7.21-7.07 (m, 1H), 4.57-4.52 (m, 2H), 3.78-3.76 (m, 1H), 2.76 -2.75 (m, 1H), 2.57 -

2.49 (m, 2H), 2.29- 2.27 (m, 2H), 1.74- 1.71 (m, 2H). -----

Ejemplo 3: Síntesis de (2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4 (trifluorometil)fenil] ácido pentanoico (Compuesto No.84).

Etapa a: Síntesis de 5-O-[tert-butil(difenil)silil]-3-deoxi-3-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol- 2-il) etil]-1,2-O-isopropilideno-β-D-lixofuranosa ----------

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Se colocó una mezcla del compuesto (0.14g), obtenida de la etapa f del Ejemplo 1, trifenilfosfina (0.080g) y ftalimida (0.045g) en un frasco de fondo redondo y se secó al vacío elevado durante 10 minutos. Se liberó el vacío bajo una atmósfera de nitrógeno y se agregó tetrahidrofurano (5mL) a la mezcla de la reacción. Se enfrió la misma a 0°C y se agregó lentamente azodicarboxilato dietilo (0.1 mL). Se agitó la mezcla de la reacción durante 30 minutos a la misma temperatura y luego se templó con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua, solución salina, se secó sobre sulfato sódico anhidro y se concentró. Se purificó el residuo así obtenido mediante columna cromatográfica sobre gel de sílice utilizando 30% de acetato de etilo en hexano como eluyente para obtener el compuesto del título (0.11g). Masa (m/z): 608 (M^+ +23). ---

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Etapa b: Síntesis de 3-deoxi-3-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-1,2-O-isopropilideno-β-D-lixofuranosa --

Se agregó a una solución del compuesto (0.060g), obtenida de la etapa a precedente, en tetrahidrofurano seco (2 mL) a 0°C, fluoruro de amoníaco tetra-butilo (0.2 mL). Se agitó la mezcla resultante inicialmetne a 0°C durante 1 hora, y luego a temperatura ambiente durante 4 horas. Se enfrió la mezcla de la reacción a 0°C, se templó con cloruro de amoníaco saturado y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina, se secó sobre sulfato sódico anhidro y se concentró. El residuo así obtenido se purificó mediante columna cromatográfica sobre gel de sílice utilizando 60% de acetato de etilo en hexano como eluyente para proporcionar el compuesto del título (0.4 g). ---------

Etapa c: Síntesis de (5S)-3-deoxi-3-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-4,5-O-isopropilideno-D-arabi-no-pentodialdo-5,2-furanosa ----------
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Se colocó en un frasco de fondo Redondo de tres cuellos, cloruro de oxalilo (0.6 mL) y diclorometano (20 mL) y se enfrió a -78°C. Se agregó dimetilsulfóxido (1mL) en gotas a la mezcla de la reacción. Se calentó la misma a -35°C durante 5 a 10 minutos y nuevamente se enfrió a -78°C. Se agregó a una solución del compuesto (1 g), obtenida de la etapa b anterior, en diclorometano (5mL) lentamente mientras se mantenía la misma temperatura. Se agitó la

mezcla de la reacción durante 45 minutos hasta que la temperatura de la reacción llegó a -35°C. Se enfrió nuevamente la misma a -78°C y se agregó trietilamina (2.4 mL). Se agitó la mezcla de la reacción durante 30 minutos adicionales y se permitió que la temperatura llegara a -35°C. Se templó la mezcla de la reacción con solución de cloruro de amoníaco saturada y se extrajo con diclorometano. Se lavó la capa orgánica combinada con agua y solución salina, se secó sobre sulfato sódico anhidro y se concentró para proporcionar el compuesto del título (1.0 g). ----------

Etapa d: Síntesis de 2-{2-[(3aS,5R,6S,6aS)-2,2-dimetil-5-{(E)-2-[4-(trifluorometil)fenil]vinil}tetrahidrofuro[2,3-d][1,3]dioxol-6-il]etil}-1H-isoindole-1,3(2H)-diona ---------

Se agregó a la suspensión de trifenil[4-(trifluorometil)bencil]bromuro de fosfonio (0.795 g) en dimetilsulfóxido (5 mL), tert-butóxido de potasio (0.292g). Se agregó una solución de compuesto (0.5 g), obtenida de la etapa c precedente, en tetrahidrofurano (7 mL) en gotas después de 20 minutos, y se agitó la mezla de la reacción durante 1 hora a la misma temperatura. Se templó la mezcla de la reacción con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida y el residuo así obtenido se purificó mediante columna cromatográfica utilizando 30% de acetato de etilo en hexano como eluyente para proporcionar el

compuesto del título (0.25g). Masa (m/z):487 (M^+) ---------

Etapa e: Síntesis de 2-{2-[(3aS,5R,6S,6aS)-2,2-dimetil-5-{2-[4-(trifluorometil)fenil]etil}tetrahidrofuro[2,3-d][1,3]dio-xol-6-il]etil}-1H-isoindole-1,3(2H)-diona ------

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Se agregó 10% de paladio sobre carbón (0.2 g) a la solución del compuesto (0.25g), obtenida de la etapa de anterior, en acetato de etilo (20 mL) a temperatura ambiente y se hidrogenó la mezcla de la reacción a 50 psi durante 4 horas en un aparato *Paar*. Se filtró la mezcla de la reacción a través de un dispositivo de filtración y el residuo se lavó con metanol. Se concentró el filtrado para conseguir el compuesto del título (0.225 g). ----------

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Etapa f: Síntesis de 2-{2-[(2R,3R,4S,5R)-4,5-dihidroxi-2-{2-[4-(trifluorometil)fenil]etil}tetrahidrofuran-3-il]etil}-1H-isoindole-1,3(2H)-diona ----------

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Se agregó ácido perclórico (0.2 mL) a una solución del compuesto (0.225 g), obtenida de la etapa e precedente, en acetonitrilo (4mL), agua (1 mL) y tetrahidrofurano (0.5 mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 55°C durante 30 minutos. Luego se templó la mezcla de la reacción utilizando bicarbonato de sodio. Se evaporaron los solventes a presión reducida. El residuo así obtenido se colocó en acetato de etilo y agua. Se separó la capa orgánica y se lavó con agua y solución salina y se secó en

sulfato sódico anhidro. Se concentró el solvente bajo presión reducida para producir el ccompuesto del título (0.22g). ----------

Etapa g: Síntesis de (1R,2S)-4-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-2-formil-1-{2-[4-(trifluorometil)fenil] etil} formato de butilo ----------

Se agregó una solución de metaperiodato de sodio (0.313 g en 1 mL de agua) a una solución del compuesto (0.22g), obtenida de la etapa f anterior, en metanol:tetrahidrofurano (3 mL:1 mL) a 0°C. Se agitó la mezcla de la reacción durante 2 horas a la misma temperatura. Después de agitar la mezcla de la reacción durante 6 horas adicionales a temperatura ambiente, se evaporó la mezcla de la reacción sobre un evaporador giratorio, y el residuo se colocó en agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida, para conseguir el compuesto del título (0.22 g). ----------

Etapa h: Síntesis de (2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-(formiloxi)-5-[4-(trifluorometil) fe-nil] ácido pentanoico ----------

Se agregó a una solución del compuesto (0.22g), obtenida de la etapa g anterior, en un solvente mezcla de

acetonitrilo:agua (3mL:1mL) a 0°C, dihidrogenfosfato de sodio (0.021g), clorito de sodio (0.081g) y peróxido de hidrógeno (1mL, 30% en agua). Se agitó la mezcla de la reacción durante 2 horas a temperatura ambiente. Se evaporaron los solventes bajo presión reducida para obtener un residuo. Se agregó acetato de etilo y agua al residuo resultante. Se separó la capa orgánica, se lavó con agua y solución salina, se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida, para conseguir el compuesto del título (0.2 g). ----------

Etapa i: Síntesis de (2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5- [4- (trifluorometil) fenil] ácido pentanoico ----------

Se agregó carbonato de potasio (0.178 g) a una solución del compuesto (0.2g), obtenida de la etapa h precedente, en metanol (7 mL) a 0°C. Se agitó la mezcla de la reacción a temperatura ambiente durante 3 horas. Se evaporaron los solventes y el residuo se colocó en agua y acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 10% de metanol en diclorometano como eluyente para conseguir el compuesto del título (0.090 g). Masa (m/z): 458.0(M^+ +23) ----------

^{1}HNMR (CD_3OD): δ 7.83 (q, 2H, J = 3.1 Hz), 7.71 (t, 2H, J = 3.2 Hz), 7.51 (d, 2H, J = 7.6 Hz), 7.28 (d, 2H, J = 7.9 Hz), 3.95-3.76 (m, 3H), 2.93-2.55 (m, 3H), 2.14-1.75 (m, 4H) ----

Ejemplo 4: Síntesis de (2R,3R)-5-(4'-clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il) etil] -3-hidroxi ácido pentanoico (Compuesto Nro. 89). ----------

Etapa a: Síntesis de 1,2:5,6-Di-O-isopropiliden-α-D-ribo-3-hexulo-furanosa ----------

Se colocó cloruro de oxalilo (25.16 mL) y diclorometano (200 mL) en un frasco de fondo redondo de tres cuellos y se enfrió a -75°C bajo atmósfera de nitrógeno. Se agregó luego dimetilsulfóxido (27.3 mL) en gotas lentamente manteniendo la temperatura a -70°C. Se agitó la mezcla de la reacción durante 30 minutos a la misma temperatura, y después se cargó diacetona-α-D-glucosa (50 g) en diclorometano (500 mL) lentamente manteniendo la temperatura a -70°C. Después de 20 minutos, se agregó trietilamina (80 mL) en gotas a la mezcla anterior a la misma temperatura. Se cargó solución de cloruro de amoníaco saturada en agua (500 mL) a la mezcla de la reacción después de 30 minutos y se permitió que la temperatura se elevara a temperatura ambiente. Se extrajo la mezcla de la reacción con diclorometano. Se secó la capa orgánica sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para conseguir el

compuesto del título (45 g). ----------

Etapa b: Síntesis de 1,2:5,6-Di-O-isopropilideno-3-deoxi-3-(2-etoxi-2-oxoetilideno)- α -D-ribo-hexofuranosa ----------

Se cargó a la suspensión de hidruro de sodio (0.155 g, 60% en aceite.) en tetrahidrofurano (5 mL) a 0^0 C, fosfonoacetato de trietilo (1.55 mL). Después de 20 minutos, se agregó una solución del compuesto (1g), obtenida de la etapa a anterior, en tetrahidrofurano (3 mL) en gotas y se agitó la mezcla de la reacción durante 1 hora a la misma temperatura. Se agregó una solución de cloruro de amoníaco saturada a la mezcla de la reacción. Se extrajo la mezcla resultante con acetato de etilo. Se secaron los extractos combinados sobre sulfato sódico anhidro y se evaporaron bajo presión reducida para producir un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 30% de acetato de etilo en hexano como eluyente para obtener el compuesto del título (1.3 g). Masa (m/z): 351.1(M^+ +23) ----------

Etapa c: Síntesis de 1,2:5,6-Di-O-isopropilideno-3-deoxi-3-(2-etoxi-2-oxoetil)- α -D-allofuranosa ----------

Se agregó 10% de paladio sobre carbón (0.05 g) a la solución del compuesto (0.15 g), obtenida de la etapa b precedente, en acetato de etilo (10 mL) a temperatura ambiente y se suministró hidrógeno a 50 psi durante 4 horas. Se filtró la mezcla de la reacción a través de un

dispositivo de filtración y se lavó el residuo con acetato de etilo. Se concentró el filtrado para conseguir el compuesto del título (0.12g). Masa (m/z): 353.2 (M^+ +1). ----------

Etapa d: Síntesis de 3-deoxi-3-(2-etoxi-2-oxoetil)-1,2-O-isopropilideno-α-D-allofuranosa ----------

Se agregó 30% de ácido perclórico (4 mL) a una solución del compuesto (2.0 g), obtenida de la etapa c anterior, en tetrahidrofurano (20 mL) a -5°C -0°C. Se agitó la mezcla de la reacción durante 5 horas a -5°C -0°C y luego se templó con solución de bicarbonato de sodio saturada (20 mL). Se evaporaron los solventes, se agregó acetato de etilo y agua al residuo resultante. Se separó la capa orgánica, se lavó con solución salina, se secó sobre sulfato sódico anhidro y se concentró para conseguir 1.5 g del compuesto del título. Masa (m/z):313.2 (M^+ +1). ----------

Etapa e: Síntesis de 3-deoxi-3-(2-etoxi-2-oxoetil)-1,2-O-isopropilideno-α-D-ribo-pentodialdo-1,4-furanosa ----------

Se agregó a una solución del compuesto (1.5 g), obtenida de la etapa d anterior, en metanol (15 mL), solución acuosa de periodato de sodio (1.65 g en 10 mL de agua) a 0°C. Se agitó la mezcla de la reacción durante 3 horas desde 0°C a temperatura ambiente. Se evaporaron los solventes. Se agregó acetato de etilo y agua al residuo. Se separó la capa orgánica, se lavó con solución salina, se secó sobre

sulfato sódico anhidro y se concentró para conseguir el compuesto del título (0.9g). Masa (m/z):259.2 (M^+ +1). ----------

Etapa f: Síntesis de etilo {(3aR,5R,6R,6aR)-5-[(E)-2-(4-bromofenil)vinil]-2,2-dimetiltetrahidrofuro[2,3-d][1,3]dioxol-6-il}acetato ----------

Se agregó a la suspensión de (4-bromobencil) trifenil-bromuro de fosfonio (2.67g) en dimetilsulfóxido (15 mL), tert-butóxido de potasio (0.508g) a 0°C. Después de agitar la mezcla de la reacción durante 30 minutos a temperatura ambiente, se agregó una solución del compuesto (0.9 g), obtenida de la etapa e anterior, en tetrahidrofurano (5 mL) en gotas a 0°C. Se agitó la mezcla de la reacción durante 2 horas desde 0°C a temperatura ambiente, y se templó con agua fría helada. Se evaporaron los solventes, y se agregó acetato de etilo y agua al residuo resultante. Se separó la capa orgánica, se lavó con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida y el residuo así obtenido se purificó mediante columna cromatográfica utilizando 10% de acetato de etilo en hexano como eluyente para proporcionar el compuesto del título (1.0 g). Masa (m/z):413.3 (M^+ +1) ----------

Etapa g: Síntesis de etilo {(3aR,5R,6R,6aR)-5-[(E)-2-(4'-clorobifenil-4-il)vinil]-2,2-dimetiltetrahidrofuro[2,3-d][1, 3]dioxol-6-il}acetato ----------

Se calentó una mezcla del compuesto (1.0g), obtenida de la etapa f precedente, (4-clorofenil) ácido borónico (0.76 g), tetraquis(trifenilfosfina)paladio (0) (0.14 g) y carbonato de potasio (1.0 g) en dimetilformamida seca (10 mL) a 110°C durante 4 horas. Se agregó acetato de etilo y agua a la mezcla de la reacción. Se separó la capa orgánica, se lavó con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel sílice utilizando 12% de acetato de etilo en hexano como eluyente para conseguir el compuesto del título (0.9 g). Masa (m/z): 465.2 (M^+ +23) ----------

Etapa h: Síntesis de etilo {(3aR,5R,6R,6aR)-5-[2-(4'-clorobifenil-4-il)etil]-2,2-dimetiltetrahidrofuro [2,3-d][1, 3]dioxol-6-il}acetato ----------

Se agregó a la solución del compuesto (0.8 g), obtenida de la etapa g anterior, en acetato de etilo (15 mL), 10% de paladio sobre carbón (0.25 g) a temperatura ambiente. Se evacuó el sistema con hidrógeno y se agitó la mezcla de la reacción durante 4 horas a temperatura ambiente bajo una atmósfera de hidrógeno. Se filtró la mezcla de la reacción a través de un dispositivo de filtración y se concentró para conseguir el compuesto del título (0.75 g). Masa (m/z): 415.4 (M^+ -28). ----------

Etapa i: Síntesis de 2-{(3aR,5R,6R,6aR)-5-[2-(4'-clorobifenil-4-il)etil]-2,2-dimetiltetrahidrofuro[2,3-d][1,3]dioxol-6-il}etanol ----------

Se agregó una solución del compuesto (0.75g), obtenida de la etapa h anterior, en tetrahidrofurano (15 mL), hidruro de alumino litio (0.096 g) a 0°C. Se agitó la mezcla de la reacción resultante durante 3 horas a la misma temperatura, y luego se agregó una solución de cloruro de amoníaco saturada. Luego se filtró la mezcla de la reacción a través de gel de sílice (100-200 mesh) y se concentró. Se agregó acetato de etilo y agua al residuo resultante. Se separó la capa orgánica, se lavó con agua y solución salina, se secó sobre sulfato sódico anhidro, se filtró, se concentró bajo presión reducida para conseguir el compuesto del título (0.65 g). Masa (m/z): 425.2 (M^+ +23). ----------

Etapa j: Síntesis de 2-{(3aR,5R,6R,6aR)-5-[2-(4'-clorobifenil-4-il) etil]-2,2-dimetiltetrahidrofuro[2,3-d][1,3]dio-xol-6-il}etil metanosulfonato ----------

Se agregó trietilamina (0.43 ml) y cloruro de metanosulfonilo (0.21 mL) a una solución del compuesto (0.6 g) obtenida de la etapa i anterior, en diclorometano (15 mL) a 0°C. Se agitó la mezcla de la reacción a temperatura ambiente durante 2 horas. Se agregó diclorometano y agua a la mezcla de la reacción. Se separó la capa orgánica, se lavó con agua, se secó y se concentró bajo presión reducida

para proporcionar el compuesto del título (0.6g). ---------

Etapa k: Síntesis de 2-(2-{(3aR,5R,6R,6aR)-5-[2-(4'-clorobi-fenil-4-il)etil]-2,2-dimetiltetrahidrofuro[2,3-d][1,3]dioxol -6-il}etil)-1H-isoindole-1,3(2H)-diona ----------

Se agregó ftalimida de potasio (0.051 g) en una porción de una solución agitada del compuesto (0.12 g), obtenida de la etapa j anterior, en dimetilformamida (5 mL) a temperatura ambiente bajo atmósfera de nitrógeno. Se calentó la solución resultante a 50 °C durante alrededor de 14 horas y luego se enfrió a temperatura ambiente. Se agregó acetato de etilo y agua a la mezcla de la reacción. Se separó la capa orgánica, se lavó con agua y solución salina, se secó sobre sulfato sódico anhidro. Se evaporó la fase orgánica hasta el secado total bajo presión reducida. De este modo el residuo así obtenido se purificó mediante columna cromatográfica utilizando 30% de acetato de etilo en hexano como eluyente para proporcionar el compuesto del título (0.1 g). Masa (m/z): 549.5 ($M^+ + NH_4^+$) ----------

Etapa l: Síntesis de 2-(2-{(2R,3S,4R,5S)-2-[2-(4'-chlorobi-fenil-4-il)etil]-4,5-dihidroxitetrahidrofurano-3-ol}etil)-1H -isoindole-1,3(2H)-diona ----------

Se agregó ácido trifluoroacético (1mL) y agua (0.5 mL) al compuesto (0.04g), obtenido de la etapa k anterior. Se agitó la mezcla de la reacción a temperatura ambiente

durante 2 horas. Se evaporaron los solventes a presión reducida. El residuo así obtenido se colocó en acetato de etilo y agua. Se separó la capa orgánica y se lavó con agua y solución salina y se secó sobre sulfato sódico anhidro. Se concentró el solvente bajo presión reducida para producir el compuesto del título (0.028 g). ----------

Etapa m: Síntesis de (2R,3R)-5-(4'-clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-(formiloxi) ácido pentanoico ----------

Se agregó a una solución del compuesto (0.028g), obtenida de la etapa 1 anterior, en *tert*-butanol:agua (2:3; 1.3 mL), metaperiodato de sodio (0.051 g) a temperatura ambiente. Se agitó la mezcla de la reacción durante 2 horas a la misma temperatura y se agregó permangnato de potasio (0.001 g) a 0°C. Después de agitar la mezcla de la reacción durante 6 horas adicionales a temperatura ambiente, la misma se evaporó sobre evaporador giratorio, se colocó el residuo en agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida, para conseguir el compuesto del título (0.025 g).

Etapa n: Síntesis de (2R,3R)-5-(4'-clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi áci-do pentanoico ----------

Se agregó carbonato de potasio (0.007g) a una solución del compuesto (0.025 g), obtenida de la etapa m precedente, en metanol (1 mL) a 0°C. Se agitó la mezcla de la reacción a temperatura ambiente durante 3 horas. Se evaporaron los solventes y se colocó el residuo en agua y acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 10% de metanol en diclorometano como eluyente para obtener el compuesto del título (0.014 g). Masa (m/z):478.2 (M^+ +1). ----------

^{1}HNMR (CD_3OD): δ7.83 (q, 2H, J = 4Hz), 7.77 (q, 2H, J = 4Hz), 7.56 (d, 2H, J = 8Hz), 7.48 (d, 2H, J = 8Hz), 7.40 (d, 2H, J = 8Hz), 7.26 (d, 1H, J = 8Hz), 3.83-3.70 (m, 3H), 2.85-2.49 (m, 3H), 1.92-1.70(m, 4H). ----------

Ejemplo 5: Síntesis de (2R,3S)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 205). ----------

Etapa a: Síntesis de 3-O-Acetil-1,2:5,6-di-O-isopropilideno-α-D-eritrohexofuran-3-enosa ----------

Se agregó anhidrido acético (65.77 mL) a una solución del compuesto (45 g), obtenida de la etapa a del Ejemplo 4, en piridina (500 mL) y se calentó la mezcla de la reacción a

60°C de la noche a la mañana. Luego se concentró la mezcla de la reacción para obtener un residuo. Se agregó acetato de etilo y agua al residuo. Se separó la capa orgánica, se lavó con ácido clorhídrico diluido, agua y solución salina. Se evaporó el solvente bajo presión reducida y el residuo así obtenido se purificó mediante columna cromatográfica de gel de sílice utilizando 8% de acetato de etilo en hexano como eluyente para proporcionar el compuesto del título (21 g). Masa (m/z): 301.19(M^+ +1). ----------

Etapa b: Síntesis de 3-O-acetil-1,2:5,6-di-O-isopropilideno-α-D-gulofuranosa ----------

Se agregó a una solución del compuesto (26 g), obtenida de la etapa a precedente, en acetato de etilo (250 mL), 10% de paladio sobre carbón (6g) y la mezcla de la reacción se agitó bajo atmósfera de hidrógeno a 60 psi durante 4 horas sobre aparato *Paar*. Se filtró la mezcla de la reacción a través de lecho de filtración. Se evaporaron los solventes para obtener un residuo crudo que se purificó usando columna cromatográfica sobre gel de sílice utilizando 15% de acetato de etilo en hexano como eluyente para proporcionar el compuesto del título (17 g). Masa (m/z): 324.97 (M^+ +Na). ---

Etapa c: Síntesis de 1,2:5,6-di-O-isopropilideno-α-D-gulofuranosa ----------

Se agregó metóxido de sodio (12.5 g) a una solución del compuesto (64 g), obtenido de la etapa b anterior, en metanol (10 mL). Se agitó la mezcla de la reacción durante 3 horas a 0°C. Luego se concentró la mezcla de la reacción. El residuo así obtenido se purificó mediante columna cromatográfica sobre gel de sílice utilizando 30% de acetato de etilo en hexano como eluyente para conseguir el compuesto del título (31 g). Masa (m/z): 261.26 (M^+ +1). ----------

Etapa d: Síntesis de 1,2:5,6-di-O-isopropilideno-α-D-xilo-hexofuranos-3-ulosa ----------

Se agregó hipoclorito de sodio (225 mL, 4% solución) en gotas a una solución del compuesto (30 g), obtenida de la etapa c anterior, seguido del agregado de 2,2,6,6,-tetrametilpiperidina N-oxilo (0.18 g), bromuro de potasio (10.62 g) y acetato de sodio (14.19 g) en acetato de etilo (300 mL) y agua (100 mL). Después de 20 min, se agregó trietilamina (3.3 mL) en gotas a la mezcla precedente a la misma temperatura. Se extrajo la mezcla de la reacción con acetato de etilo después de 30 min. Se secó la capa orgánica sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para conseguir el compuesto del título (10.4 g). ----------

Etapa e: Síntesis de 1,2:5,6-Di-O-isopropilideno-3-deoxi-3-(2-etoxi-2-oxoetilideno)-α-D-xilo-hexofuranosa ----------

Se agregó a la solución del compuesto (10.5 g), obtenida de la etapa d anterior, en tetrahidrofurano, trifenil-fosforano carboetoximetileno (27 g). Se sometió a reflujo la mezcla de la reacción durante 2 horas y se concentró para conseguir el compuesto crudo, que se purificó mediante columna cromatográfica sobre gel sílice utilizando 8% de acetato de etilo en hexano como eluyente para producir el compuesto del título (5.0 g). Masa (m/z): 350.28 (M^+ +Na) ---

Etapa f: Síntesis de 1,2:5,6-Di-O-isopropilideno-3-deoxi-3-(2-etoxi-2-oxoetil)-α-D-gulofuranosa ----------

Se agregó 10% de paladio sobre carbon (3 g) a la solución del compuesto (12 g), obtenida de la etapa e anterior, en metanol (50 mL) y se agitó la mezcla de la reacción bajo atmósfera de hidrógeno a temperatura ambiente durante 4 horas. Se filtró la mezcla de la reacción a través de un dispositivo de filtración y se lavó el residuo utilizando acetato de etilo. Se concentró el filtrado para suministrar el compuesto del título (12 g). Masa (m/z): 330.9 (M^+ +1). --

Etapa g: Síntesis de 1,2:5,6-Di-O-isopropilideno-3-deoxi-3-(2-hidroxietil)-α-D-gulofuranosa ----------

Se agregó a la suspensión de hidruro de aluminio litio (2.37 g) en tetrahidrofurano (120 mL). una solución del compuesto (12 g), obtenida de la etapa f precedente, en tetrahidrofurano (100 mL) a -50°C. Se permitió que la

mezcla de la reacción llegara a la temperatura de 0°C y se agitó la mezcla durante 30 minutos a 0°C. Se templó la mezcla de la reacción utilizando solución de cloruro de amoníaco acuosa (25 mL). Se permitió que la mezcla de la reacción llegara lentamente a temperatura ambiente y asimismo se agitó durante otras 12 horas a la misma temperatura. Se filtró la mezcla de la reacción a través de un dispositivo de filtración, se lavó el residuo con acetato de etilo. Se secó la capa orgánica sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener el compuesto del título (8.5 g). ----------

Etapa h: Síntesis de 1,2:5,6-Di-O-isopropilideno-3-deoxi-3-[2-(1,3-dioxol,3-dihidro-2H-isoindol-2-il)etil]-α -D-gulofu-ranosa ----------

Se colocó una mezcla del compuesto (8.5 g), obtenida de la etapa g precedente, trifenilfosfina (21.83g) y ftalimida (6.73 g) en un frasco de fondo redondo y se secó al vacío elevado durante 10 minutos. Se liberó el vacío bajo una atmósfera de nitrógeno y se agregó tetrahidrofurano (100 mL) a la mezcla de la reacción. Se enfrió la misma a 0°C y se agregó azodicarboxilato diisopropilo (12.625 g) lentamente. Se agitó la mezcla de la reacción durante 30 minutos a la misma temperatura y luego se templó con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua, solución salina, se secó sobre sulfato sódico anhidro y se concentró. El residuo así obtenido se purificó mediante columna cromatográfica sobre gel de sílice

utilizando 40% de acetato de etilo en hexano como eluyente para conseguir el compuesto del título (8.5 g). ----------

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Etapa i: Síntesis de 3-deoxi-3-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-1,2-O-(isopropilideno)-α-D-gulofuranosa

Se agregó 30% de ácido perclórico (8.15 mL) a una solución del compuesto (0.8 g) obtenida de la etapa h anterior, en tetrahidrofurano (200 mL). Se agitó la mezcla de la reacción durante 2 horas a 0-5°C y luego se templó con solución de carbonato de hidrógeno sódico saturada. Se agregó acetato de etilo y agua a la mezcla resultante. Se separó la capa orgánica, se lavó con solución salina, se secó sobre sulfato sódico anhidro y se concentró. El residuo así obtenido se purificó mediante columna cromatográfica sobre gel de sílice utilizando 60% de acetato de etilo en hexano para obtener 5.5 g del compuesto del título. Masa (m/z): 377.24 (M^+ +1) --

Etapa j: Síntesis de (5R)-3-deoxi-3-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-4,5-O- (1-metiletilideno) - L-arabino-pentodialdo-5,2-furanosa ----------

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Se agregó a una solución del compuesto (5.5 g), obtenido en la etapa i anterior, en acetona (100 mL), solución de periodato sódico acuosa (9.33 g en 100 mL) a 0°C. Se agitó la mezcla de la reacción durante 2 horas, luego se filtró y se concentró. El residuo así obtenido se colocó en agua y se extrajo con acetato de etilo. Se secó la capa orgánica

sobre sulfato sódico y se concentró para conseguir el compuesto del título (5.2 g). ----------

Etapa k: Síntesis de 2-(2-{(3aR,5S,6R,6aR)-5-[(E)-2-(4-bromofenil)etenil]-2,2-dimetiltetrahidrofuro[2,3-d][1,3]dio-xol-6-il}etil)-1H-isoindole-1,3(2H)-diona ----------

Se agregó una solución de (4-bromobencil) trifenilfosfonio (13.3 g) en sulfóxido de dimetilo (10 mL) en gotas a la suspensión de hidruro de sodio (1 g de 50% suspensión) en sulfóxido de dimetilo (20 mL) a 0°C. Después de 20 minutos, se agregó una solución del compuesto (6 g), obtenida de la etapa j anterior, en dimetilsulfóxido (100 mL) en gotas y se agitó la mezcla de la reacción durante 1 hora a la misma temperatura. Se templó la mezcla de la reacción con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 40% de acetato de etilo en hexano para proporcionar el compuesto del título (5.5 g). Masa (m/z): 499.10 (M^+ +1). ----------

Etapa l: Síntesis de 2-(2-{(3aR,5S,6R,6aR)-5-[(E)-2-(3'-fluoro-4'-metilbifenil-4-il)etenil]-2,2-dimetiltetrahidrofu-ro[2,3-d][1,3]dioxol-6-il}etil)-1H-isoindole-1,3(2H)-diona -

Se secó una mezcla del compuesto (0.5 g), obtenido de la etapa k anterior, 3-fluoro-4-metilfenil ácido borónico (0.314 g), tetraquistrifenilfosfinopaladio (0) (0.057 g) y carbonato de potasio (0.414 g) al vacío elevado durante 10 minutos. Se liberó el vacío bajo atmósfera de nitrógeno y se agregó dimetilformamida seca (5 mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 120°C durante 2 horas, y luego se templó con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 30% de etilacetato en hexano como eluyente para conseguir el compuesto del título (0.37 g). Masa (m/z): 527.23 (M^+ +1) ----------

Etapa m: Síntesis de 2-(2-{(3aR,5S,6R,6aR)-5-[2-(3'-fluoro-4'-metilbifenil-4-il)etil]-2,2-dimetiltetrahidrofuro [2,3-d] [1,3]dioxol-6-il}etil)-1H-isoindole-1,3(2H)-diona ----------

Se agregó 10% de paladio sobre carbón (100 g) a la solución del compuesto (0.37g), obtenida de la etapa l anterior, en acetato de etilo (10 mL) a temperatura ambiente y se hidrogenó la mezcla de la reacción a la presión de 35 psi durante 1 hora en un aparato *Paar*. Se filtró la mezcla de la reacción a través de un dispositivo de filtración y se lavó el residuo con metanol. Se concentró el filtrado para obtener el compuesto del título (0.28 g). ----------

Etapa n: Síntesis de 2-(2-{(2S,3S,4R,5S)-2-[2-(3'-fluoro-4'-metilbifenil-4-il)etil]-4,5-dihidroxitetrahidrofuran-3-il} etil)-1H-isoindole-1,3(2H)-diona ----------

Se agregó a una solución del compuesto (0.28 g), obtenida de la etapa m anterior, en acetonitrilo (20 mL) y agua (2 mL), 30% de ácido perclórico (0.4 mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 55°C durante 30 minutos. Luego se templó la mezcla de la reacción utilizando solución de bicarbonato de sodio. Se evaporaron los solventes a presión reducida. El residuo así obtenido se colocó en acetato de etilo y agua. Se separó la capa orgánica y se lavó con agua y solución salina y se secó sobre sulfato sódico anhidro. Se concentró el solvente bajo presión reducida para producir el compuesto del título (0.418 g) en la forma de masa cruda que se utilizó de nuevo sin ninguna purificación y caracterización. ----------

Etapa o: Síntesis de (2R,3S)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5- (3'-fluoro-4'-metilbifenil-4-il)-3-(formiloxi) ácido pentanoico ----------

Se agregó una solución de metaperiodato de sodio (0.489 g en 5 mL de agua) a una solución del compuesto (0.4 g), obtenida de la etapa n anterior, en *tert*-butanol:tetrahidrofurano (5 mL: 5 mL) a 0°C. Se agitó la mezcla de la reacción durante 2 horas a la misa temperatura y se agregó permangnato de potasio (0.033 g) a 0°C. Después

de agitar la mezcla de la reacción durante 6 horas más a temperatura ambiente, se evaporó la mezcla de la reacción sobre evaporador giratorio, se colocó el residuo en agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida, para conseguir el compuesto del título (0.31 g) como una masa cruda que se utilizó de nuevo sin purificación y caracterización. ----------

Etapa p: Síntesis de (2R,3S)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hi-droxi ácido pentanoico ----------

Se agregó a una solución del compuesto (0.31g), obtenida de la etapa o anterior, en metanol (5 mL), carbonato de potasio (0.094 g) a 0°C. Se agitó la mezcla de la reacción a temperatura ambiente durante 3 horas. Se diluyó la mezcla de la reacción con acetato de etilo (50 mL), se acidificó con sulfato de hidrógeno sódico y se lavó con agua (20 mL). Se secó la capa orgánica sobre sulfato sódico anhidro y se concentró bajo presión reducida para obtener un residuo que se purificó mediante cromatografía de capa delgada preparativa utilizando 10% de metanol en diclorometano como eluyente para obtener el compuesto del título (0.020 g). Masa (m/z): 476.07 (M^+ +1). ----------

^{1}HNMR (CD_3OD): δ 7.72-7.64 (m, 4H), 7.36-7.34 (m, 2H), 7.18-7.10 (m, 5H), 3.68-3.61 (m, 3H), 2.75-2.71 (m, 1H),

2.55-2.49 (s, 1H), 2.32-2.30 (m, 1H), 2.16 (s, 3H), 1.99-1.94 (m, 2H), 1.70-1.62 (m, 2H). ----------

Ejemplo 6: Síntesis de (2*S*,3*S*)-3-hidroxi-5-(4'-metoxibifenil -4-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 208). ----------

Etapa a: Síntesis de 5-O-[tert-butil(difenil)silil]-3-deoxi-1,2-O-isopropilideno-3-[2- (4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-α-L-ribofuranosa ----------

Se secó una mezcla del compuesto (20 g), obtenida de la etapa f del Ejemplo 1, trifenilfosfina (17.6 g) y 1,2,3-benzotriazin-4(3*H*)-ona (7.2 g) al vacío elevado en un frasco de fondo redondo durante 10 minutos. Se liberó el vacío bajo atmósfera de nitrógeno y se agregó tetrahidrofurano (200 mL) a la mezcla de la reacción precedente. Se enfrió la mezcla de la reacción a 0°C y se agregó lentamente azodicarboxilato diisopropilo (9.8 mL). Se agitó la mezcla de la reacción durante 30 minutos a la misma temperatura, y luego se templó con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua, solución salina, se secó sobre sulfato sódico anhidro y se concentró para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 30% de etilacetato en hexano como eluyente para conseguir el compuesto del título (22 g). Masa (m/z): 586.24 (M^+ +1). ----------

Etapa b: Síntesis de 3-deoxi-1,2-O-isopropilideno-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-α-L-ribofuranosa ----

Se agregó a una solución del compuesto (22 g), obtenida de la etapa a anterior, en tetrahidrofurano seco (200 mL) a 0°C, 1 M de solución de fluoruro de tetra-butilamoníaco (75 mL). Se agitó la mezcla resultante inicialmente a 0°C durante 1 hora y luego a temperatura ambiente durante 4 horas. Se enfrió la mezcla de la reacción a 0°C, se templó con cloruro de amoníaco saturado y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina, se secó sobre sulfato sódico anhidro y se concentró. El residuo así obtenido se purificó mediante columna cromatográfica sobre gel de sílice utilizando 50% de acetato de etilo en hexano como eluyente para proporcionar el compuesto del título (6.5 g). Masa (m/z): 348.25(M^+ +1). ----------

Etapa c: Síntesis de (5S)-3-deoxi-4,5-O-isopropilideno-3-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-D-ribo-pentodialdo-5,2-furanosa ----------

Se agregó a la solución del compuesto (6.5 g), obtenida de la etapa b anterior, en diclorometano seco (100 mL), enfriado a 0°C, reactivo periodinano *Dess-Martin* (11.1 g). Se permitió agitar la mezcla de la reacción durante 2 horas. Se templó la mezcla de la reacción con tiosulfato de sodio y carbonato de hidrógeno sódico. Se agregó diclorometano a la mezcla de la reacción. Se separó la capa

orgánica, se lavó con agua y solución salina, se secó sobre sulfato de sodio y se evaporó para proporcionar el compuesto del título. (6.5g)

Etapa d: Síntesis de 3-(2-{(3aS,5S,6S,6aS)-5-[(E)-2-(4-bromofenil)vinil]-2,2-dimetiltetrahidrofuro[2,3-d][1,3]dioxol-6-il}etil)-1,2,3-benzotriazin-4(3H)-ona ----------

Se agregó a la suspensión de hidruro de sodio (0. 979 g, 60% en aceite) en sulfóxido de dimetilo (60 mL), enfriada a 0°C, (4-bromobencil) bromuro de trifenilfosfonio (14.5 g). Se agregó al compuesto (6.5 g), obtenido de la etapa c anterior, en tetrahidrofurano (60 mL) en gotas después de 20 minutos, y se agitó la mezcla de la reacción durante 1 hora a la misma temperatura. Se templó la mezcla de la reacción con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida y el residuo así obtenido se purificó mediante columna cromatográfica utilizando 40% de acetato de etilo en hexano como eluyente para proporcionar el compuesto del título (4 g). Masa (m/z): 498.19(M^+ +1). ----------

Etapa e: Síntesis de 3-(2-{(3aS,5S,6S,6aS)-5-[(E)-2-(4'-metoxibifenil-4-il)vinil]-2,2- dimetiltetrahidrofuro [2,3-d] [1,3]dioxol-6-il}etil)-1,2,3-benzotriazin-4(3H)-ona ----------

Se secó una mezcla del compuesto (1g), obtenida de la etapa d anterior, 4-metoxifenil ácido borónico (0.61 g), paladio

tetraquistrifenilfosfina (0) (0.232 g) y carbonato de potasio (0.832 g) al vacío elevado durante 10 minutos y se agregó dimetilformamida seca (20 mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 120°C durante 2 horas, y luego se templó con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 50% de acetato de etilo en hexano como eluyente para obtener el compuesto del título (0.62 g). Masa (m/z): 526.41(M^+ +1). ----------

Etapa f: Síntesis de 3-(2-{(3aS,5S,6S,6aS)-5-[2-(4'-metoxibifenil-4-il)etil]-2,2-dimetiltetrahidrofuro[2,3-d][1, 3]dioxol-6-il}etil)-1,2,3-benzotriazin-4(3H)-ona ----------

Se agregó a la solución del compuesto (0.62 g), obtenida de la etapa e anterior, en un solvente mezcla de acetato de etilo (20 mL), 10% de paladio sobre carbón (0.3 g) a temperatura ambiente y se hidrogenó la mezcla de la reacción a la presión de 35 psi durante 4 horas en un aparato *Paar*. Se filtró la mezcla de la reacción a través de un dispositivo de filtración y se lavó el residuo con metanol. Se concentró el filtrado para obtener el compuesto del título (0.6 g). ----------

Etapa g: Síntesis 3-(2-{(2S,3R,4S,5R)-4,5-dihidroxi-2-[2-(4'-metoxibifenil-4-il)etil]tetrahidrofurano-3-il}etil)-1,2, 3-benzotriazin-4(3H)-ona ----------

Se agregó ácido perclórico (0.2 mL) a una solución del compuesto (0.6 g), obtenida de la etapa f anterior, en acetonitrilo (50 mL) y agua (10 mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 55°C durante 30 minutos. Luego se templó la mezcla de la reacción utilizando solución de carbonato de hidrógeno sódico. Se evaporaron los solventes a presión reducida. El residuo así obtenido se colocó en acetato de etilo y agua. Se separó la capa orgánica y se lavó con agua y solución salina y se secó sobre sulfato sódico anhidro. Se concentró el solvente bajo presión reducida para producir el compuesto del título (0.6 g). ----------

Etapa h: Síntesis de (2S,3S)-3-(formiloxi)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5- (4-pirimidin-5-ilfenil) ácido pentanoico. ----------

Se agregó a una solución del compuesto (0.6 g), obtenida de la etapa g anterior, en *tert*-butanol:tetrahidrofurano (7 mL: 7 mL) a 0°C una solución de metaperiodato sódico (0.973 g en 7 mL de agua). Se agitó la mezcla de la reacción durante 2 horas a la misma temperatura y se agregó permangnato de potasio (0.036 g) a 0°C. Después de agitar la mezcla de la reacción durante 6 horas adicionales a

temperatura ambiente, se evaporó la mezcla de la reacción, se colocó el residuo en agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener el compuesto del título (0.5 g). ----------

Etapa i: Síntesis de (2S,3S)-3-hidroxi-5-(4'-metoxibifenil-4 -il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico ----------

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Se agregó carbonato de potasio (0.151 g) a una solución del compuesto (0.5 g), obtenida de la etapa h anterior, en metanol (5 mL) y tetrahidrofurano (5 mL) a 0°C. Se agitó la mezcla de la reacción a temperatura ambiente durante 3h. Se evaporaron los solventes y se colocó el residuo en agua y acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante cromatografía de capa delgada preparativa utilizando 10% de metanol en diclorometano como eluyente para obtener el compuesto del título (0.008g). Masa (m/z): 474.31 (M^+ +1); ^{1}HNMR (CD_3OD): ð 8.32-7.87 (m, 5H), 7.50-7.42 (m, 4H), 7.24-7.20 (m, 2H), 6.97-6.94 (m, 1H), 4.60-4.50 (m, 2H), 3.81 (s, 3H), 3.59 (br t, 1H), 3.0-1.8 (m, 7H). ----------

Ejemplo 7: Síntesis de (2*S*,3*R*)-3-hidroxi-5-[4-(5-metil-piridin-2-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-

il) etil]ácido pentanoico (Compuesto Nro. 209). ----------

Etapa a: Síntesis de 4-(5-metilpiridin-2-il)benzaldehido --

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Se secó una mezcla de 2-bromo-5-metilpiridina (2g), (4-formilfenil) ácido borónico (3.5g), tetraquistrifenilfosfinopaladio (0) (0.672 g) y carbonato de potasio (4.8 g) al vacío elevado durante 10 minutos y se agregó dimetilformamia seca (15 mL) a temperatura ambiente. Se calentó la mezcla de la reacción a 110°C durante 6 horas, y luego se templó con agua y se extrajo con acetato de etilo. Se lavó la capa orgánica con agua y solución salina y se secó sobre sulfato sódico anhidro. Se evaporó el solvente bajo presión reducida para obtener un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 20% de etilacetato en hexano como eluyente para conseguir el compuesto del título (2.8 g). Masa (m/z): 198.20 ----------

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Etapa b: Síntesis de etil(2E)-3-[4-(5-metilpiridin-2-il) fenil]prop-2-enoato ----------

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A la suspensión de hidruro de sodio (0.682 g, 60% en aceite.) en tetrahidrofurano (20 mL) a 0°C se cargó fosfonoacetato trietilo (3.82 g). Después de 15 minutos, se agregó una solución del compuesto (2.8 g), obtenida de la etapa a anterior, en tetrahidrofurano (5mL) en gotas y se agitó la mezcla de la reacción durante 30 minutos a

temperatura ambiente. Se agregó una solución de cloruro de amoníaco saturada en agua a la mezcla de la reacción. Se evaporó el solvente y se extrajo la mezcla resultante con acetato de etilo. Se secaron los extractos combinados sobre sulfato sódico anhidro y se evaporó bajo presión reducida para producir un residuo que se purificó mediante columna cromatográfica sobre gel de sílice utilizando 15% de etilacetato en hexano como eluyente para obtener el compuesto del título (1.8 g). ----------

Etapa c: Síntesis de etil3-[4-(5-metilpiridin-2-il) fenil] propanoato ----------

Se agregó 10% de paladio sobre carbón (0.8 g) a la solución del compuesto (1.8 g), obtenida de la etapa b anterior, en tetrahidrofurano (15 mL) a temperatura ambiente y se suministró hidrógeno a una presión de 50 psi (aparato *Paar*) durante 4 horas. Se filtró la mezcla de la reacción a través de un dispositivo de filtración y se concentró para obtener el compuesto del título (1.8 g). ----------

Etapa d: Síntesis de 3-[4-(5-metilpiridin-2-il)fenil]propan-1-ol. ----------

Se agregó a la suspensión de hidruro de aluminio litio (0.424 g) en tetrahidrofurano (20 mL), una solución del compuesto (2 g), obtenida de la etapa c anterior, en tetrahidrofurano (10 mL) a -20°C. Se agitó la mezcla de la

reacción durante 2 horas a -30°C y se agregó una solución de sulfato de sodio saturada a la misma temperatura. Luego se filtró la mezcla de la reacción a través de un dispositivo de filtración y el residuo se lavó con acetato de etilo. Se secó la capa orgánica sobre sulfato sódico anhidro, se filtró, se concentró bajo presión reducida y el residuo así obtenido se purificó mediante columna cromatográfica sobre gel de sílice utilizando 50% de etilacetato en hexano como eluyente para obtener el compuesto del título (1.2 g). -----

Etapa e: Síntesis de 3-[4-(5-metilpiridin-2-il)fenil] propanal ----------

Se agregó a una solución agitada del compuesto (1.4g), obtenida de la etapa d anterior, en diclorometano (20 mL), 2,2,6,6,-tetrametilpiperidina N-oxilo (9.6 mg), y bromuro de potasio (73.4 mg) a 0°C bajo atmósfera de nitrógeno. Se agregó hipoclorito de sodio (13.7 mL, 4% solución) enseguida a un pH de 8-9 (mantenido con el agregado de solución de bicarbonato de sodio acuoso). Se agitó la reacción durante 20 min a 0^0C. Se separó la capa orgánica y se extrajo la capa acuosa con diclorometano. Se lavaron las capas orgánicas combinadas con solución de bicarbonato de sodio saturada acuosa, agua y solución salina. Se secó la capa orgánica sobre sulfato sódico anhidro, se filtró, se concentró bajo presión refucida para obtener aldehido crudo (0.9 g). ------

Etapa f: Síntesis de 3-{(3S,4R)-3-{[(4S)-4-bencil-2-oxo-1,3-tiazolidin-3-il]carbonil}-4-hidroxi-6-[4-(5-metilpiridin-2-il)fenil]hexil}-1,2,3-benzotriazin-4(3H)-ona

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En un frasco secado al fuego, se colocó 3-{4-[(4S)-4-bencil-2-oxo-1,3-tiazolidin-3-il]-4-oxobutil}-1,2,3-benzotriazin-4 (3H)-ona (1.18 g) en diclorometano (10 mL) y se enfrió a 0°C. Se agregó tetracloruro de titanio (3.4 mL) en diclorometano (6 mL) en gotas y se agitó la mezcla de la reacción durante 10-15 minutos. Se agregó (-)-Sparteina (1.7g) lentamente a la mezcla de la reacción y se agitó a 0°C durante 45 minutos. Se agregó a una solución del compuesto (0.65 g), obtenida de la etapa e anterior, en diclorometano (10 mL) lentamente y en agitación continua a 0°C. Después de 3 horas, se templó la reacción con agregado en gotas de solución de cloruro de amoníaco saturada y diclorometano. Se separó la capa orgánica y se extrajo la capa acuosa con diclorometano. Se lavó la capa orgánica con solución salina, y se secó sobre sulfato sódico anhidro, y se concentró bajo presión reducida. El producto crudo así obtenido se purificó mediante columna cromatográfica *flash* de gel se sílice utilizando 30% de acetato de etilo en hexano como eluyente para obtener el aducto aldol (0.56 g).

Etapa g: Síntesis de (2S,3R)-3-hidroxi-5-[4-(5-metilpiridin-2-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico ----------

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Se agregó a una solución en agitación del compuesto (0.2 g), obtenida de la etapa f anterior, en tetrahidrofurano:agua (3:1, 10 mL) a 0°C, solución de peróxido de hidrógeno acuosa (30%, 0.16 mL), seguida del agregado de monohidrato de hidróxido de litio (0.02g) en agua (5 mL). Se agitó la mezcla de la reacción a 0°C durante 30 minutos. Se concentró la mezcla de la reacción y se extrajo el residuo con acetato de etilo. Se acidificó la capa acuosa con sulfato de hidrógeno sódico y se extrajo con acetato de etilo. Se lavaron las capas combinadas con agua, solución salina y se secaron sobre sulfato sódico anhidro. Se evaporaron los solventes bajo presión reducida y el residuo crudo se purificó mediante columna cromatográfica *flash* de gel de sílice utilizando 3% de metanol en diclorometano como eluyente para obtener el compuesto del título (0.035 g). Masa (m/z): 459.21(M^+ +1); ^{1}HNMR (CD_3OD): δ 8.40 (s, 1H), 8.30 (d, 1H, J = 7.88 Hz), 8.15 (d, 1H, J = 8Hz), 8.05-7.70 (m, 6H), 7.27 (d, 2H, J = 7.6 Hz), 4.40-4.0 (m, 2H), 3.80-3.60 (m, 1H), 2.80-2.40 (m, 5H), 2.38(s, 3H), 1.80-1.60 (m, 2H). ----------

Ejemplo 7A: Síntesis de (2S,3R)-3-hidroxi-5-[4-(6-metoxi-piridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]ácido pentanoico (Compuesto Nro. 86). ----------

Etapa a: Síntesis de metil (2*E*)-3-(4-bromofenil)prop-2-enoato ----------

Se agregó a una solución en agitación de 4-ácido bromocinámico (16g) en metanol (150 mL) cloruro de tionilo (30 mL) a 0°C. Se calentó la mezcla de la reacción a temperatura ambiente y se sometió a reflujo durante 3 horas. Después de enfriar a temperatura ambiente se evaporaron los solventes hasta secado total. Se utilizó el compuesto crudo obtenido como tal para la siguiente etapa. ----------

Etapa b: Síntesis de metil(2*E*)-3-[4-(6-metoxipiridin-3-il) fenil]prop-2-enoato ----------

Se colocó el compuesto (7.5 g) obtenido de la etapa a anterior, piridina-2-metoxi-5-ácido borónico (9.48 g), tetraquistrifenilfosfinopaladio (0) (1.79 g) y carbonato de potasio (12.83 g) en dimetilformamida (60 mL) bajo atmósfera de nitrógeno. Se sometió a reflujo la mezcla de la reacción bajo atmósfera de nitrógeno durante 6 horas. Después de enfriar a temperatura ambiente, se agregó agua y se extrajo la mezcla de la reacción con acetato de etilo. Se lavaron las capas orgánicas combinadas con agua y solución salina, se secó sobre sulfato sódico anhidro y se evaporaron los solventes bajo presión reducida. Se purificó el producto crudo mediante columna cromatográfica *flash* de gel de sílice utilizando 20-30% de acetato de etilo en hexano para obtener el compuesto del título (8.09 g). ----------

Etapa c: Síntesis de metil3-[4-(6-metoxipiridin-3-il)fenyl] propanoato ----------

Se agregó a la solución del compuesto (8.1 g), obtenida de la etapa b anterior, en una mezcla de acetato de etilo /metanol/tetrahidrofurano (~300 mL), 10% de paladio sobre carbón (1.6 g) y se agitó bajo atmósfera de hidrógeno a la presión de 30 psi (aparato *Paar*) durante 2.5 horas. Se filtró la mezcla de la reacción a través de un dispositivo de filtración se lavó con acetato de etilo y se concentró el filtrado bajo presión reducida para obtener el compuesto del título como un sólido blanco que se utilizó como tal para la siguiente etapa. ----------

Etapa d: Síntesis de 3-[4-(6-metoxipiridin-3-il)fenil] ácido propanoico ----------

Se agregó a una solución en agitación de hidruro de aluminio litio (2.28 g) en tetrahidrofurano (120 mL) el compuesto (8g), obtenido de la etapa c anterior en tetrahidrofurano (50 mL) a 0°C. Se agitó la mezcla de la reacción a 0°C durante 3 horas. Se templó la mezcla de la reacción cuidadosamente con solución de cloruro de amoníaco saturada, se realizó filtración, se lavó con acetato de etilo. Se separaron las capas orgánicas, se lavaron con solución salina y se secaron sobre sulfato sódico anhidro y se evarporaron los solventes bajo presión reducida. Se purificó el producto crudo mediante columna cromatográfica

flash de gel de sílice utilizando 20-30% de acetato de etilo en hexano para obtener el compuesto del título como un sólido cristalino blanco (5.1 g). ----------

Etapa e: Síntesis de 3-[4-(6-metoxipiridin-3-il)fenil] propanal ----------

Se agregó a una solución en agitación del compuesto (9.0 g) obtenida de la etapa d anterior, en diclorometano (90 ml), 2,2,6,6,-N-oxil tetrametilpiperidina (58.77 mg) y bromuro de potasio (447.57 mg) a 0°C bajo atmósfera de nitrógeno. Se agregó hipoclorito de sodio acuoso 4% (3.497 g) enseguida a un pH de 8-9 (mantenido mediante el agregado de solución de bicarbonato de sodio acuoso saturado). Se agitó la mezcla de la reacción durante 20 minutos a 0°C. Luego, se separó la capa orgánica y se extrajo la capa acuosa con diclorometano. Se lavaron las capas orgánicas combinadas con solución de bicarbonato de sodio acuoso saturada, agua y solución salina. Finalmente, se secaron las capas orgánicas sobre sulfato sódico anhidro y se concentró bajo presión reducida para conseguir aldehido crudo (8.1g) que se utilizó como tal en la siguiente etapa. ----------

Etapa f: Síntesis de 3-{(3*S*,4*S*)-3-{[(4*S*)-4-bencil-2-oxo-1,3-tiazolidin-3-il]carbonil}-4-hidroxi-6-[4-(5-metoxipiridin-2-il)fenil]hexil}-1,2,3-benzotriazin-4(3*H*)-ona ----------

Se colocó en un frasco secado al fuego, 3-{4-[(4S)-4-bencil-2-oxo-1,3-tiazolidin-3-il]-4-oxobutil}-1,2,3-benzotriazin-4 (3H)-ona (2.0 g) en diclorometano (10 mL) y se enfrió a 0°C. Se agregó tetracloruro de titanio (0.619 mL) en diclorometano (6 mL) en gotas y se agitó la mezcla de la reacción durante 10-15 minutos. Se agregó lentamente(-)-Sparteina (2.7 mL) a la mezcla de la reacción y se agitó a 0°C durante 45 minutos. Se agregó una solución del compuesto (1.34 g), obtenida de la etapa e anterior, en diclorometano (10 mL) lentamente y continuó la agitación a 0^{0}C. Después de 3 horas, se templó la reacción y se agregó con la adición en gotas de solución de cloruro de amoníaco saturada y diclorometano. Se separó la capa orgánica y se extrajo la capa acuosa con diclorometano. Se lavó la capa orgánica con solución salina, y se secó sobre sulfato sódico anhidro, y se concentró bajo presión reducida. El producto crudo así obtenido se purificó mediante columna cromatográfica *flash* de gel de sílice utilizando 30% de acetato de etilo en hexanos como eluyentes para conseguir el aducto aldol (1.21g). ----------

Etapa g: Síntesis de (2*S*,3*R*)-3-hidroxi-5-[4-(5-metoxipiridin -2-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4*H*)-il) etil] ácido pentanoico ----------

Se agregó a una solución en agitación del compuesto (1.21 g), obtenida de la etapa f anterior, en tetrahidrofurano: agua (3:1, 15 mL) a 0°C, solución de peróxido de hidrógeno acuoso (30%, 1.02 mL), seguido del agregado de monohidrato

de hidróxido de litio (114.5mg) en agua (5 mL). Se agitó la mezcla de la reacción a 0°C hasta la conclusión de la hidrólisis. Se concentró la mezcla de la reacción y se extrajo el residuo con acetato de etilo. Se acidificó la capa acuosa con sulfato de hidrógeno sódico y se extrajo con acetato de etilo. Se lavaron las capas combinadas con agua, solución salina y se secaron sobre sulfato sódico anhidro. Se evaporaron los solventes bajo presión reducida y el residuo crudo se purificó mediante columna cromatográfica *flash* de gel de sílice utilizando 3% de metanol en diclorometano como eluyente para conseguir el compuesto del título (0.61 g). Masa (m/z): 474.87(M^+ +1); ^{1}H NMR (400 MHz, MeOD): δ 8.32- 8.30 (2H, m), 8.16- 8.14 (1H, m), 8.04- 8.03 (1H, m), 7.92- 7.88 (2H, m), 7.46 (2H, d, J = 8Hz), 7.24 (2H, m, J = 8Hz), 6.86 (1H, d, J = 8Hz), 4.57- 4.53 (2H, m), 3.93 (3H, s), 3.78-3.83 (1H, m), 2.83-2.80 (1H, m), 2.63- 2.60 (1H, m), 2.52- 2.49 (1H, m), 2.32-2.28 (2H, m), 1.80- 1.76 (2H, m). ----------

Ejemplo 7B: Síntesis de (2*S*,3*R*)-5-(2',4'-difluorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Compuesto Nro. 216). ----------

Etapa a: Síntesis de metil(2*E*)-3-(4-bromofenil)prop-2-enoato. ----------

Se agregó a una solución agitada de 4-ácido bromocinámico (16g) en metanol (150 mL), cloruro de tionilo (30 mL) a

0°C. Se calentó la mezcla de la reacción a temperatura ambiente y se sometió a reflujo durante 3 horas. Después de enfriar a temperatura ambiente, se evaporaron los solventes hasta el secado total. El compuesto crudo obtenido se utilizó como tal para la etapa siguiente. ----------

Etapa b: Síntesis de metil (2*E*)-3-(3',5'-difluorobifenil-4-il)prop-2-enoato ----------

Se colocó el compuesto (0.75 g) obtenido de la etapa a anterior, 2,4 difluorofenil ácido borónico (0.737 g), tetraquistrifenilfosfinopaladio (0) (0.07 g) y carbonato de potasio (1.28 g) en dimetilformamida (6 mL) bajo atmósfera de nitrógeno. Se sometió a reflujo la mezcla de la reacción bajo atmósfera de nitrógeno durante 6 horas. Después de enfriar a temperatura ambiente, se agregó agua y se extrajo la mezcla de la reacción con acetato de etilo. Se lavaron las capas orgánicas combinadas con agua y solución salina, se secaron sobre sulfato sódico anhidro y se evaporaron los solventes bajo presión reducida. Se purificó el producto crudo bajo bajo columna cromatográfica *flash* de gel de sílice utilizando 20-30% de acetato de etilo en hexano para obtener el compuesto del título (0.810 g). ----------

Etapa c: Síntesis de metal 3-(3',5'-difluorobifenil-4-il) propanoato ----------

Se agregó a la solución del compuesto (0.79 g), obtenida de la etapa b anterior, en una mezcla de acetato de etilo (~10 mL), 10% de paladio sobre carbón (0.2g) y se agitó bajo atmósfera de hidrógeno a una presión de 30 psi durante 2.5 horas. Se filtró la mezcla de la reacción a través de un dispositivo de filtración, se lavó con acetato de etilo y se concentró el filtrado bajo presión reducida para obtener el compuesto del título (0.77g) como sólido blanco que se utilizó como tal para la siguiente etapa. ----------

Etapa d: Síntesis de 3-(3',5'-difluorobifenil-4-il)ácido propanoico ----------

Se agregó a una solución en agitación de hidruro de aluminio litio (0.2 g) en tetrahidrofurano (15 mL) el compuesto (0.77g), obtenido de la etapa c anterior en tetrahidrofurano (50 mL) a 0°C. Se agitó la mezcla de la reacción a 0°C durante 3 horas. Se templó la mezcla de la reacción cuidadosamente con solución de cloruro de amoníaco saturada, se realizó filtración, se lavó con acetato de etilo. Se separaron las capas orgánicas, se lavaron con solución salina y se secaron sobre sulfato sódico anhidro y se evaporaron los solventes bajo presión reducida. Se purificó el producto crudo mediante columna cromatográfica *flash* de gel de sílice utilizando 20-30% de acetato de etilo en hexano para obtener el compuesto del título como un sólido cristalino blanco (0.70 g). ----------

Etapa e: Síntesis de 3-(3',5'-difluorobifenil-4-il)propanal.

Se agregó a una solución en agitación del compuesto (0.7g), obtenida de la etpa d anterior, en diclorometano (10 mL), 2,2,6,6,-N-oxil tetrametilpiperidina (4.36 mg), y bromuro de potasio (33.32 mg) a 0°C bajo atmósfera de nitrógeno. Se agregó hipoclorito de sodio (6.5mL, 4% solución) enseguida a un pH de 8-9 (mantenido mediante agregado de solución de bicarbonato de sodio acuosa). Se agitó la mezcla de la reacción durante 20 min a 0°C. Se separó la capa orgánica y se extrajo la capa acuosa con diclorometano. Se lavaron las capas orgánicas combinadas con solución de bicarbonato de sodio acuoso saturada, agua y solución salina. Se secó la capa orgánica sobre sulfato sódico anhidro, se filtró, se concentró bajo presión reducida para obtener aldehido crudo (0.57 g). ----------

Etapa f: Síntesis de 3-[(2*R*,3*S*)-2-{[(4*S*)-4-bencil-2-oxo-1,3-tiazolidin-3-il]carbonil}-5- (3',5'-difluorobifenil-4-il)-3-hidroxipentil]-1,2,3-benzotriazin-4(3*H*)-ona ----------

Se colocó en un frasco secado al fuego, 3-{3-[(4*S*)-4-bencil-2-oxo-1,3-tiazolidin-3-il]-3-oxopropil}-1,2,3-benzotriazin-4(3*H*)-ona (0.25 g) en diclorometano (10 mL) y se enfrió a 0°C. Se agregó tetracloruro de titanio (0.76 mL, 1M solución) en gotas y se agitó la mezcla de la reacción durante 10-15 minutos. Se agregó (-)-Sparteina (0.36 mL) lentamente a la mezcla de la reacción y se agitó

a 0°C durante 20 minutos. Se agregó una solución del compuesto (0.187 g), obtenida de la etapa e precedente, en diclorometano (10 mL) y continuó agitándose a 0°C. Después de 3 horas, se templó la reacción con agregado de gotas de solución de cloruro de amoníaco saturada y diclorometano. Se separó la capa orgánica y se extrajo la capa acuosa con diclorometano. Se lavó la capa orgánica con solución salina, y se secó sobre sulfato sódico anhidro, y se concentró bajo presión reducida. El producto crudo así obtenido se purificó mediante columna cromatográfica *flash* de gel de sílice utilizando 30% de acetato de etilo en hexano como eluyentes para conseguir el aducto aldol (0.24g). ----------

Etapa g: Síntesis de (2*S*,3*R*)-5-(3',5'-difluorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico ----------

Se agregó a una solución del compuesto (0.2g), obtenida de la etapa f precedente, en tetrahidrofurano:agua (3:1, 10 mL) a 0°C, solución de peróxido de hidrógeno acuosa (30%, 0.16 mL), seguida del agregado de monohidrato de hidróxido de litio (19.53mg) en agua (2 mL). Se agitó la mezcla de la reacción a 0°C hasta que se completó la hidrólisis. Se concentró la mezcla de la reacción y se extrajo el residuo con acetato de etilo. Se acidificó la capa acuosa con sulfato de hidrógeno sódico y se extrajo con acetato de etilo. Se lavaron las capas combinadas con agua, solución salina y se secaron sobre sulfato sódico anhidro. Se evaporaron los solventes bajo presón reducida y el residuo

crudo se purificó mediante columna cromatográfica *flash* de gel de sílice utilizando 10% de metanol en diclorometano como eluyente para conseguir el compuesto del título (0.090g). Masa (m/z): 466.06 (M^+ +1); ^{1}HNMR (CD_3OD): δ 8.17-8.8.15 (m, 1H), 8.05-8.01(m, 1H), 7.90-7.88 (m, 1H), 7.86-7.84 (m, 1H), 7.46-7.42 (m, 2H,), 7.40-7.29 (m, 2H,), 7.03-6.98 (m, 2H), 4.82-4.84 (m, 2H), 3.94 (s, 1H), 3.22 - 3.21 (m, 1H), 2.91-2.89 (m, 1H), 2.78-2.75 (m, 1H), 1.94-1.90 (m, 2H). ----------

Ejemplo 7C: Síntesis de (2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Compuesto Nro. 217). ----------

Etapa a: Síntesis de metil (2*E*)-3-(4-bromofenil)prop-2-enoato ----------

Se agregó a una solución agitada de 4-ácido bromocinámico (16g) en metanol (150 mL), cloruro de tionilo (30 mL) a 0°C. Se calentó la mezcla de la reacción a temperatura ambiente y se sometió a reflujo durante 3 horas. Después de enfriar a temperatura ambiente se evaporaron los solventes hasta el secado total. Se utilizó el compuesto crudo obtenido como tal para la siguiente etapa. ----------

Etapa b: Síntesis de metil (2*E*)-3-(4'-fluorobifenil-4-il) prop-2-enoato ----------

Se colocó el compuesto (0.75 g) obtenido de la etapa a precedente, 4-fluorofenil ácido borónico (0.65 g), tetraquistrifenilfosfinopaladio (0) (0.07 g) y carbonato de potasio (1.28 g) en dimetilformamida (6 mL) bajo atmósfera de nitrógeno. Se sometió a reflujo la mezcla de la reacción bajo atmósfera de nitrógeno durante 6 horas. Después de enfriar a temperatura ambiente, se agregó agua y se extrajo la mezcla de la reacción con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua y solución salina, se secaron sobre sulfato sódico anhidro y se evaporaron los solventes bajo presión reducida. Se purificó el producto crudo mediante columna cromatográfica *flash* de gel de sílice uitlizando 20-30% de acetato de etilo en hexano para obtener el compuesto del título (0.720 g). ----------

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Etapa c: Síntesis de metil 3-(4'-fluorobifenil-4-il) propanoato ----------

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Se agregó a la solución del compuesto (0.7 g), obtenida de la etapa b precedente, en una mezcla de acetato de etilo (~20 mL), 10% de paladio sobre carbón (0.2 g) y se agitó bajo atmósfera de hidrógeno a la presión de 30 psi (aparato *Paar* apparatus) durante 2.5 horas. Se filtró la mezcla de la reacción a través de un dispositivo de filtración con acetato de etilo y se concentró el filtrado bajo presión reducida para obtener el compuesto del título (0.7g) como un sólido blanco que se utlizó como tal para la siguiente etapa. ----------

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Etapa d: Síntesis de 3-(4'-fluorobifenil-4-il)ácido propanoico ----------

Se agregó a una solución agitada de hidruro de aluminio litio (0.2 g) en tetrahidrofurano (15 mL) el compuesto (0.7g), obtenido de la etapa c anterior en tetrahidrofurano (50 mL) a 0°C. Se agitó la mezcla de la reacción a 0°C durante 3 horas. Se templó la mezcla de la reacción cuidadosamente con solución de cloruro de amoníaco saturada, se sometió a filtración, se lavó con acetato de etilo. Se separaron las capas orgánicas, se lavó con solución salina y se secó sobre sulfato sódico anhidro y se evaporaron los solventes bajo presión reducida. Se purificó el producto crudo mediante columna cromatográfica *flash* de gel de sílice utilizando 20-30% de acetato de etilo en hexano para obtener el compuesto del título como un sólido cristalino blanco (0.70 g). ----------

Etapa e: Síntesis de 3-(4'-fluorobifenil-4-il) propanal ---

Se agregó a una solución agitada del compuesto (0.7g), obtenida de la etapa d precedente, en diclorometano (10 mL), 2,2,6,6,-N-oxil tetrametilpiperidina (4.74 mg), y bromuro de potasio (36.05 mg) a 0°C bajo atmósfera de nitrógeno. Se agregó hipoclorito de sodio (0.28g, 4% solución) enseguida a un pH de 8-9 (mantenido por el agregado de solución de bicarbonato de sodio acuosa). Se agitó la reacción durante 20 min a 0°C. Se separó la capa

orgánica y la capa acuosa se extrajo con diclorometano. Se lavaron las capas orgánicas combinadas con solución de bicarbonato de sodio acuosa, agua y solución salina. Se secó la capa orgánica sobre sulfato sódico anhidro, se filtró, se concentró bajo presión reducida para obtener aldehido crudo (0.55 g). ----------

Etapa f: Síntesis de 3-[(2*R*,3*S*)-2-{[(4*S*)-4-bencil-2-oxo-1,3-tiazolidin-3-il]carbonil}-5-(4'-fluorobifenil-4-il)-3-hidro-xipentil]-1,2,3-benzotriazin-4(3*H*)-ona ----------

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Se colocó en un frasco secado al fuego, 3-{3-[(4*S*)-4-bencil-2-oxo-1,3-tiazolidin-3-il]-3-oxopropil}-1,2,3-benzotriazin-4 (3*H*)-ona (0.25 g) en diclorometano (10 mL) y se enfrió a 0°C. Se agregó tetracloruro de titanio (0.76 mL, 1M solución) en gotas y se agitó la mezcla de la reacción durante 10-15 minutos. Se agregó lentamente (-)-Sparteina (0.36 mL) a la mezcla de la reacción y se agitó a 0°C durante 20 minutos. Se agregó lentamente a una solución del compuesto (0.17 g), obtenida de la etapa e anterior, en diclorometano (10 mL) y se continuó agitando a 0°C. Después de 3 horas, se templó la reacción con el agregado de gotas de solución de cloruro de amoníaco saturada y diclorometano. Se separó la capa orgánica y se extrajo la capa acuosa con diclorometano. Se lavó la capa orgánica con solución salina, y se secó sobre sulfato sódico anhidro, y se concentró bajo presión reducida. El producto crudo así obtenido se purificó mediante columna cromatográfica *flash* de gel de sílice utilizando 30% de acetato de etilo en

hexanos como eluyentes para obtener el aducto aldol (0.2g).

Etapa g: Síntesis de (2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico ----------

Se agregó a una solución agitada del compuesto (0.18 g), obtenida de la etapa f anterior, en tetrahidrofurano:agua (3:1, 10 mL) a 0°C, solución de peróxido de hidrógeno acuosa (30%, 0.15 mL), seguida del agregado de monohidrato hidróxido de litio (17.6mg) en agua (2 mL). Se agitó la mezcla de la reacción a 0°C hasta completar la hidrólisis. Se concentró la mezcla de la reacción y se extrajo el residuo con acetato de etilo. Se acidificó la capa acuosa con sulfato de hidrógeno de sodio y se extrajo con acetato de etilo. Se lavaron las capas combinadas con agua, solución salina y se secó sobre sulfato sódico anhidro. Se evaporaron los solventes bajo presión reducida y se purificó el residuo crudo mediante columna cromatográfica *flash* de gel de sílice utilizando 10% de metanol en diclorometano como eluyente para obtener el compuesto del título (0.075 g). Masa (m/z): 448.07 (M^+ +1); ^{1}HNMR (CD_3OD): δ 8.25-8.8.30 (d, 1H, J = 8Hz), 8.15-8.12 (d, 1H, J = 8Hz), 8.05-8.00 (t, 1H, J = 8Hz), 7.89-7.85 (t, 1H, J = 8Hz), 7.58-7.55 (m, 1H,), 7.47-7.45 (d, 1H J = 8Hz), 7.28- 7.26 (d, 1H, J = 8Hz), 7.89-7.87 (m, 1H), 7.61 (m, 2H), 7.53-7.59 (m,1H), 7.30-7.25 (d, 2H J = 8Hz), 7.15- 7.11 (t, 2H, J = 8Hz), 4.81-4.79 (m, 2H), 3.92 (s, 1H), 3.22-3.16 (m,

1H), 2.92- 2.90 (m, 1H), 2.75- 2.73 (m, 1H), 1.93- 1.87 (m, 2H). ----------

Se prepararon los siguientes compuestos empleando procedimientos en la forma prevista en los Ejemplos 1 a 7C descriptos precedentemente: ----------

Se prepararon los compuestos Nros. 1 a 81, 86-88, 90-95, 97-119, 121-142, 144-203, 211-213 y 226-232 siguiendo el Ejemplo 1; se prepararon los compuestos Nros. 82-83 siguiendo el Ejemplo 2; se prepararon los compuetos Nros. 84-85 y 204 siguiendo el Ejemplo 3; se prepararon los compuestos Nros. 89 y 96 siguiendo el Ejemplo 4; se prepararon los compuestos Nros. 120 y 205-207 siguiento el Ejemplo 5; se prepararon los compuestos Nros. 143 y 208 siguiendo el Ejemplo 6; y se prepararon los compuestos Nros. 86, 209-210 y 214-225 siguiendo el Ejemplo 7. ----------

Los compuestos específicos, adecuados para su uso, preparados en el presente invento, son los enumerados a continuación: ----------

(2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil]-5-(4-pirimidin-5-ilfenil) ácido pentanoico (Compuesto Nro.1), Masa (m/z):446.0 (M^+ +1); ----------

(2S,3R)-2-[2-(5-tert-butil-1,3-dioxo-1,3-dihidro-2H-isoindol -2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-

il)fenil] áci-do pentanoico (Compuesto Nro. 2), Masa (m/z): 531.09 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-[4-(6-metilpiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 3), Masa (m/z): 458.82(M^+ +1); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5 -(4'-fluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 4), ----------

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-2-[2- (1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 5), Masa (m/z): 479.70(M^+ +1); ----------

(2S,3R)-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]-2- [2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)ethyl] ácido pentanoico (Compuesto Nro. 6), Masa (m/z):458.94 (M^+ +1); ----------

(2S,3R)-3-hidroxi-2- [2- (5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[4-(6-metilpiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 7), Masa (m/z): 472.87 (M^+ +1); --

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1, 3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil] ácido pentanoico (Compuesto Nro. 8), ----------

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4H)-il)etil] ácido pentanoico

(Compuesto Nro. 9), Masa (m/z):461.87 (M^+ +1); ----------

(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 10), Masa (m/z):473.79 (M^+ +1); ----------

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(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(5-me-til-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil] ácido pen-tanoico (Compuesto Nro. 11), Masa (m/z):493.81 (M^+ +1); -----

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo -1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 12), Masa (m/z): 479.77(M^+ +1); ----------

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(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Com-puesto Nro. 13), Masa (m/z):473.86 (M^+ +1); ----------

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(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-[4'-(trifluorometoxi)bifenil-4-il]ácido pentanoi-co (Compuesto Nro. 14), Masa (m/z):510.66 (M^+ -18); ---------

(2S,3R)-5-(4'-cloro-3'-fluorobifenil-4-il)-3-hidroxi-2-[2-(4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 15), Masa (m/z):496.10 (M^+ +1); ----------

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(2S,3R)-2-[2-(5-tert-butil-1,3-dioxo-1,3-dihidro-2H-isoindol -2-il)etil]-5-(3',4'-difluorobifenil-4-il)-3-

hidroxi ácido pentanoico (Compuesto Nro. 16), Masa (m/z):536.11 (M^+ +1); --

(2S,3R)-2-[2-(5-tert-butil-1,3-dioxo-1,3-dihidro-2H-isoindol -2-il)etil]-3-hidroxi-5-(4'-metoxibifenil-4-il)ácido penta-noico (Compuesto Nro. 17), Masa (m/z):530.09 (M^+ +1); -------

(2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido pentanoico (Compuesto Nro. 18), Masa (m/z): 512.04(M^+ +1); ----------

(2S,3R)-2-[2-(5-tert-butil-1,3-dioxo-1,3-dihidro-2H-isoindol -2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxi ácido pen-tanoico (Compuesto Nro. 19), Masa (m/z):518.14 (M^+ +1); -----

(2S,3R)-2-[2-(5-tert-butil-1,3-dioxo-1,3-dihidro-2H-isoindol -2-il)etil]-5-(4'-clorobifenil-4-il)-3-hidroxi ácido penta-noico (Compuesto Nro. 20), Masa (m/z):534.09 (M^+); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-[4'-(trifluorometil)bifenil-4-yl]ácido pentanoico (Compuesto Nro. 21), Masa (m/z):512.08 (M^+ +1); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-(4'-metilbifenil-4-il)ácido pentanoico (Compuesto Nro. 22), Masa (m/z): 458.14(M^+ +1); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5 -(3'-fluoro-4'-metoxibifenil-4-il)-3-hidroxi ácido

pentanoi-co (Compuesto Nro. 23), Masa (m/z): 492.07(M^+ +1); ----------

(2S,3R)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]ácido pen-tanoico (Compuesto Nro. 24), Masa (m/z):489.11 (M^+ +1); -----

(2S,3R)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(4-oxo-1,2,3 -benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 25), Masa (m/z):458.14 (M^+ +1); ---------- ----------

(2S,3R)-5-(4'-etilbifenil-4-i)-3-hiroxi2-[2-(4-oxo- 1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 26), Masa (m/z): 472.15(M^+ +1); ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1,3 -dioxo-1,3-dihidro-2H-isoindol-2-il) etil] ácido pentanoico (Compuesto Nro. 27), Masa (m/z):492.08 (M^+ +1); ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2- (4-oxo-1,2, 3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 28), Masa (m/z):478.09 (M^+ +1); ---------- ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-(4-pirimidin-5-ilfenil)ácido pentanoico (Compuesto Nro. 29), Masa (m/z):446.12 (M^+ +1); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil]ácido

pentanoi-co (Compuesto Nro. 30), Masa (m/z): 448.25 (M^+ +1); ---------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-(4-piridin-3-ilfenil) ácido pentanoico (Compuesto Nro. 31), Masa (m/z): 445.23(M^+ +1); ----------

(2S,3R)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil] -3-hi-droxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 32), Masa (m/z):502.19 (M^+ +1); --

(2S,3R)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoi-co (Compuesto Nro. 33), Masa (m/z):489.0(M^+ +1); ----------

(2S,3R)-3-hidroxi-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4-(6-metilpiridin-3-il) fenil] ácido penta-noico (Compuesto Nro. 34), Masa (m/z):473.0(M^+ +1); --------

(2S,3R)-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil] ácido pentanoico (Compuesto Nro. 35), Masa (m/z): 448.0 (M^+ +1); ----------

(2S,3R)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4-(6-metoxipiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 36), Masa (m/z): 505.0 (M^+ +1); -----

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil] -3-hidroxi-5-[4-(6-metoxipiridin-3-il) fenil] ácido

pentanoico (Compuesto Nro. 37), Masa (m/z):509.0 (M^+ +1); ---

(2S,3R)-3-hidroxi-2-{2-[7-(6-metoxipiridin-3-il)-4-oxo-1,2,3-benzotriazin-3(4H)-il]etil}-5-[4-(6-metoxipiridin-3-il)fe-nil]ácido pentanoico (Compuesto Nro. 38), Masa (m/z):582.0 (M^+ +1); ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-(4H)-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 39), Masa (m/z): 511.0 (M^+ +1); --

(2*S*,3*R*)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) e-til]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido pen-tanoico(Compuesto Nro. 40), Masa (m/z): 493.3(M^+ +1); ------

(2S,3R)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 41), Masa (m/z):489.0 (M^+ +1); ----------

(2S,3R)-3-hidroxi-2-{2-[5-(6-metoxipiridin-3-il)-4-oxo-1,2, 3-benzotriazin-3(4H)-il]etil}-5- [4- (6-metoxipiridin-3-il) fenil]ácido pentanoico (Compuesto Nro. 42), Masa (m/z): 582.0(M^+ +1); ----------

(2S,3R)-5-(4'-cloro-3'-fluorobifenil-4-il)-2-[2- (1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoi-co (Compuesto Nro. 43), Masa (m/z):519.0 (M^+ +23); ----------

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(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4-(1-isobutil-1H-pirazol-4-il)fenil]ácido penta-noico (Compuesto Nro. 44), Masa (m/z):490.0 (M^+ +1); --------

(2S,3R)-5-bifenil-4-il-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoin-dol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 45), Masa (m/z): 444.0 (M^+ +1); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 46), Masa (m/z):476.0 (M^+ +1); ----------

(2S,3R)-5-(3,3'-difluoro-4'-metoxibifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compueso Nro. 47), Masa (m/z):510.0 (M^+ +1); ----

(2S,3R)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil] -2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi áci-do pentanoico (Compuesto Nro. 48), Masa (m/z):502.0 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4-(1H-tetrazol-1-il)fenil]ácido pentanoico (Com-puesto Nro. 49), Masa (m/z): 458.0 (M^+ +23); --------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 50), Masa (m/z):493.0 (M^+ +1); --

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 51), Masa (m/z): 498.0 (M^+ +23); ----------

(2S,3R)-3-hidroxi-5-[4-(1-isobutil-1H-pirazol-4-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 52), Masa (m/z):490.0 (M^+ +1); ----------

(2S,3R)-5-bifenil-4-il-3-hidroxi-2- [2- (4-oxo-1,2,3-benzo-triazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 53), Masa (m/z):444.0 (M^+ +1); ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoi-co (Compuesto Nro. 54), Masa (m/z): 489.34(M^+ +1) ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5 -[6-(3-fluoro-4-metoxifenil)piridin-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 55), Masa (m/z): 493.16(M^+ +1); --

(2S,3R)-5-(4'-cloro-3-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1, 3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 56), Masa (m/z): 496.13 (M^+ +1); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-[6-(4-metoxifenil)piridin-3-il]ácido pentanoico (Compuesto Nro. 57), Masa (m/z): 475.13 (M^+ +1); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-(3-fluoro-4'-metoxibifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 58), Masa (m/z): 492.13 (M^+ +1);

(2S,3R)-5-[6-(4-clorofenil)piridin-3-il]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 59), Masa (m/z):479.12 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)ácido pentanoico (Compuesto Nro. 60), Masa (m/z): 476.16 (M^+ +1);

(2S,3R)-5-[4-(4-clorofenil)-2-tienil]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 61), Masa (m/z):484.0 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)-2-tienil]ácido penta-noico (Compuesto Nro. 62), Masa (m/z): 481.0(M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-{4-[4-(trifluorometil)fenil]-2-tienil}ácido pen-tanoico (Compuesto Nro. 63), Masa (m/z):518.0 (M^+ +1);

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[4-(3-fluoro-4-metoxifenil)-2-tienil]-3-hidroxi ácido pen-tanoico (Compuesto Nro. 64), Masa (m/z): 498.0 (M^+ +1);

(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido penta-noico (Compuesto Nro. 65), Masa (m/z):526.0 (M^+ +1); --------

(2S,3R)-3-hidroxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido penta-noico (Compuesto Nro. 66), Masa (m/z):526.0 (M^+ +1); --------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3 (4H)-il) e-til]-3-hidroxi-5-(4'-metilbifenil-4-il) ácido pentanoico (Compuesto Nro. 67), Masa (m/z): 492.0(M^+ +1); ----------

(2S,3R)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido pentanoico (Compuesto Nro. 68), Masa (m/z): 542.29(M^+ +1); ----

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin -3 (4H)-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 69), Masa (m/z):548.54 (M^+ +1); --

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5 -[2-fluoro-5-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 70), Masa (m/z): 493.30(M^+ +1); --

(2S,3R)-5-(4'-cloro-4-fluorobifenil-3-il)-2-[2-(1,3-dioxo-1, 3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 71), Masa (m/z):495.72 (M^+ +1); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[6-fluoro-4'-(trifluorometil)bifenil-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 72), Masa (m/z):530.13 (M^+ +1); --

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[4-fluoro-3-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 73), Masa (m/z):493.37 (M^+ +1); --

(2S,3R)-5-(4'-cloro-6-fluorobifenil-3-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 74), Masa (m/z):496.26 (M^+ +1); ----------

(2S,3R)-5-(3',6-difluoro-4'-metoxibifenil-3-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 75), Masa (m/z):509.77 (M^+ +1); --

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)e-til]-3-hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Compuesto Nro. 76), Masa (m/z): 492.56(M^+ +1); ----------

(2S,3R)-5-(4'-fluorobifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 77), Masa (m/z):480.0 (M^+ +1); ----------

(2S,3R)-3-hidroxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-[4-(1-metil-1H-pirazol-4-il)fenil]ácido penta-noico (Compuesto Nro. 78), Masa (m/z): 462.19 (M^+ +1); ------

(2S,3R)-2-[2-(5-cloro-1,3-dioxo-1,3-dihidro-2H -isoindol -2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 79), Masa (m/z):546.32 (M^+ +1); --

(2S,3R)-2-[2-(4-fluoro-1,3-dioxo-1,3-dihidro-2H-isoindol -2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 80), Masa (m/z):529.25 (M^+ +1); --

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 81), Masa (m/z): 498.27(M^+ +1); ----------

(2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)e-til]-5-fenil ácido pentanoico (Compuesto Nro. 82); Masa (m/z):368.0 (M^+ +1); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-fenil ácido pentanoico (Compuesto Nro. 83), Masa (m/z): 368.07 (M^+ +1); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-[4(trifluorometil)fenil]ácido pentanoico (Compuesto Nro.84), Masa (m/z): 458.0(M^+ +23); ----------

(2S,3R)-5-(4-tert-butilfenil)-2-[2-(1,3-dioxo-1,3-dihidro-2H -isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro.85), Masa (m/z):424.0 (M^+ +1); ----------

(2S,3R)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 86), Masa (m/z): 474.87(M^+ +1); ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro -2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Com-puesto Nro. 87), Masa (m/z): 478.09(M^+ +1); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro.88), Masa (m/z): 474.88(M^+ +1); ----------

(2R,3R)-5-(4'-clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro -2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Com-puesto Nro. 89), Masa (m/z):478.2 (M^+ +1); ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 *H*)-il)etil]-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]ácido penta-noico (Compuesto Nro. 90), Masa (m/z): 462.32(M^+ +1); -------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]ácido pen-tanoico (Compuesto Nro. 91), Masa (m/z): 478.38(M^+ +1); -----

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3 (4H)-il)e-til]-5-(3',4'-difluorobifenil-4-il)-3-hidroxi ácido penta-noico (Compuesto Nro. 92), Masa (m/z): 514.20(M^+ +1); ----

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3 (4H) -il)e-til]-3-hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Compuesto Nro. 93), Masa (m/z): 508.29(M^+ +1); ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3 (4H) -il)e-til]-5-(4'-fluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 94), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3 (4H) -il)e-til]-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 95), Masa (m/z): 493.37(M^+ +1); -------

(2*R*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 96), Masa (m/z): 474.87(M^+ +1); ----------

(2S,3R)-5-(2',4'-difluorobifenil-4-il)-2-[2- (1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 97), Masa (m/z): 480.13(M^+ +1); ----------

(2S,3R)-2-[2-(6-cloro-4-oxo-1,2,3-benzotriazin-3 (4H) -il)e-til]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 98), Masa (m/z): 482.15 (M^+ +1); -

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3 (4H) -il)e-til]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 99), Masa (m/z): 482.15(M^+ +1); --

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-(4'-isopropilbifenil-4-il)ácido pentanoico (Com-puesto Nro. 100), Masa (m/z): 486.18(M^+ +1); ----------

(2S,3R)-5-(3'-cloro-4'-fluorobifenil-4-il)-2-[2- (1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoi-co (Compuesto Nro. 101), Masa (m/z): 496.12(M^+ +1); ----------

(2S,3R)-5-(4'-butilbifenil-4-il)-3-hidroxi-2-[2- (4-oxo-1,2, 3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 102), Masa (m/z): 500.42(M^+ +1); ----------

(2S,3R)-5-(2'-fluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 103), Masa (m/z): 462.32(M^+ +1); ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H) -il)e-til]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 104), Masa (m/z): 466.31(M^+ +1); -

(2S,3R)-3-hidroxi-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pen-tanoico (Compuesto Nro. 105), Masa (m/z): 462.38(M^+ +1); ----

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-{6-[4-(trifluorometil)fenil]piridin-3-il} ácido pentanoico (Compuesto Nro. 106), Masa (m/z): 513.35(M^+ +1); -

(2S,3R)-5-[6-(3,4-difluorofenil)piridin-3-il]-2-[2-(1,3-dio-xo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 107), Masa (m/z): 481.32(M^+ +1); -

(2S,3R)-5-[6-(4-cloro-3-fluorofenil)piridin-3-il]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 108), Masa (m/z): 497.30(M^+ +1); -

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[6-(4-fluorofenil)piridin-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 109), Masa (m/z): 463.35(M^+ +1); ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[6-(3-fluoro-4-metilfenil)piridin-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 110), Masa (m/z): 477.34(M^+ +1); -

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 111), Masa (m/z): 482.38(M^+ +1); -

(2S,3R)-2-[2-(8-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 112), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] áci-do pentanoico (Compuesto Nro. 113), Masa (m/z):

484.39(M^+ +1); ----------

(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-[4'-(trifluorometoxi)bifenil-4-il] ácido pen-tanoico (Compuesto Nro. 114), Masa (m/z): 542.36(M^+ +1); ----

(2S,3R)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2- (7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 115), Masa (m/z): 472.12(M^+ +1); ----------

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 116), Masa (m/z):476.23(M^+ +1); ----------

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(7-me-til-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 117), Masa (m/z): 494.24(M^+ +1); ----------

(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 118), Masa (m/z): 473.38(M^+ +1); ----------

(2S,3R)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil] -3-hi-droxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 119), Masa (m/z): 516.28(M^+ +1); ----------

(2*R*,3*S*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 120), Masa (m/z): 474.87(M^+ +1); ----------

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il) ácido pentanoico (Compuesto Nro. 121), Masa (m/z): 510.23(M^+ +1); ----

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)ácido penta-noico (Compuesto Nro. 122), Masa (m/z): 510.23(M^+ +1); ------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il) ácido pentanoico (Compuesto Nro. 123), Masa (m/z): 512.31(M^+ +1); -

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 124), Masa (m/z): 490.30(M^+ +1); ------

(2S,3R)-3-hidroxi-5-[4-(1-isobutil-1H-pirazol-4-il)fenil]-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 125), Masa (m/z): 504.33(M^+ +1); -

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il) ácido pen-tanoico (Compuesto Nro. 126), Masa (m/z): 510.23(M^+ +1); ----

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(8-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 127), Masa (m/z): 492.26 (M^+ +1); ----------

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(8-me-toxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoi-co (Compuesto Nro. 128), Masa (m/z): 510.30 (M^+ +1); --------

(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(8-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 129), Masa (m/z): 504.38 (M^+ +1); ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-{6-[4-(trifluorometil)fenil] piridin-3-il} ácido pentanoico (Compuesto Nro. 130), Masa (m/z): 547.29 (M^+ +1); ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-3-hidroxi-5-{6-[4-(trifluorometil)fenil] piridin-3-il}ácido pentanoico (Compuesto Nro. 131), Masa (m/z): 549.30 (M^+ +1); ----------

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-{6-[4-(trifluorometil)fenil] piridin-3-il} ácido pentanoico (Compuesto Nro. 132), Masa (m/z): 547.29 (M^+ +1); ----------

(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-{6-[4-(trifluorometil)fenil]piridin-3-il} áci-do pentanoico (Compuesto Nro. 133), Masa (m/z): 527.40 (M^+ +1); ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-{6-[4-(trifluorometil)fenil]piridin-3-il} ácido pentanoico (Compuesto Nro. 134), Masa (m/z): 531.36 (M^+ +1); ----------

(2S,3R)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-(4'-metilbifenil-4-il)ácido pentanoico (Com-puesto Nro. 135), Masa (m/z): 488.34 (M^+ +1); --------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pen-tanoico (Compuesto Nro. 136), Masa (m/z): 494.33 (M^+ +1); ---

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il) ácido pentanoico (Compuesto Nro. 137), Masa (m/z): 494.33(M^+ +1); ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(4'-metilbifenil-4-il)ácido pentanoico (Compuesto Nro. 138), Masa (m/z): 476.30 (M^+ +1); ---------

(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido

pentanoico (Com-puesto Nro. 139), Masa (m/z): 496.30 (M^+ +1); ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 140), Masa (m/z): 476.35 (M^+ +1); ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido penta-noico (Compuesto Nro. 141), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido penta-noico (Compuesto Nro. 142), Masa (m/z): 490.34(M^+ +1); ------

(2*S*,3*S*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 143), Masa (m/z): 475.21(M^+ +1); ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 144), Masa (m/z): 512.32 (M^+ +1);

(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(6,7-difluoro-4-oxo-1, 2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 145), Masa (m/z): 514.37(M^+ +1); ----------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(8 -metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido

penta-noico (Compuesto Nro. 146), Masa (m/z): 506.38 (M^+ +1); -----

(2S,3R)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil] -3-hi-droxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H) -il)e-til]ácido pentanoico (Compuesto Nro. 147), Masa (m/z): 532.38(M^+ +1); ----------

(2S,3R)-5-[4-(6-cloropiridin-3-il)fenil]-3-hidroxi-2- [2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 148), Masa (m/z): 479.36 (M^+ +1); -------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido pentanoico (Compuesto Nro. 149), Masa (m/z): 542.11(M^+ +1); --

(2S,3R)-3-hidroxi-2-[2-(7-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il] ácido pen-tanoico (Compuesto Nro. 150), Masa (m/z): 542.11(M^+ +1); ----

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-(4'-metilbifenil-4-il)ácido pentanoico (Com-puesto Nro. 151), Masa (m/z): 488.09 (M^+ +1); -------

(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(6-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 152), Masa (m/z): 504.06 (M^+ +1); -------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil] -3-hidro-xi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 153), Masa (m/z): 493.01(M^+ +1); ------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(7-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] áci-do pentanoico (Compuesto Nro. 154), Masa (m/z): 523.02 (M^+ +1); ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-2- [2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 155), Masa (m/z): 511.04(M^+ +1); ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidro-xi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 156), Masa (m/z): 507.05 (M^+ +1); ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 157), Masa (m/z):507.05 (M^+ +1); -

(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(7-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 158), Masa (m/z): 504.09 (M^+ +1); --------

(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 159), Masa (m/z): 508.03(M^+ +1); ----------

(2S,3R)-3-hidroxi-2-[2-(7-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 160), Masa (m/z): 505.11(M^+ +1); ----

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(7-me-toxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 161), Masa (m/z): 510.04(M^+ +1); ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4-(6-metoxipiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 162), Masa (m/z): 505.11(M^+ +1); ------

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3 (4H) -il)e-til]-5-[2-fluoro-4-(6-metoxipiridin-3-il) fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 163), Masa (m/z): 526.95(M^+ +1); ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin- 3(4H)-il)etil]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidro-xi ácido pentanoico (Compuesto Nro. 164), Masa (m/z): 529.00 (M^+ +1); ---------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-

il)etil] ácido pentanoico (Compuesto Nro. 165), Masa (m/z): 507.03(M^+ +1); -

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 166), Masa (m/z): 476.01(M^+ +1); ----------

(2S,3R)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoi-co (Compuesto Nro. 167), Masa (m/z): 489.05(M^+ +1); ----------

(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 168), Masa (m/z): 488.06 (M^+ +1); ----------

(2S,3R)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 169), Masa (m/z): 472.03(M^+ +1); ----------

(2S,3R) -5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 170), Masa (m/z): 491.98 (M^+ +1); ----------

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(6-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 171), Masa (m/z): 492.00(M^+ +1); ----------

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(6-me-toxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido

pentanoico (Compuesto Nro. 172), Masa (m/z): 509.98(M^+ +1);

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4'-(trifluorometoxi)bifenil-4-il]ácido pen-tanoico (Compuesto Nro. 173), Masa (m/z): 557.99 (M^+ +1); ---

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(6 -metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 174), Masa (m/z): 506.04(M^+ +1); ------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3 (4H)-il) e-til]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 175), Masa (m/z): 526.91(M^+ +1); ----------

(2S,3R)-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)-2-tienil]-2 -[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 176), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidro-xi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H) -il)etil] ácido pentanoico (Compuesto Nro. 177), Masa (m/z): 523.01(M^+ +1); ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 178), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 179), Masa (m/z): 489.07(M^+ +1); ------

(2S,3R)-5-[4-(2-cloropiridin-3-il)fenil]-3-hidroxi-2- [2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 180), Masa (m/z): 508.99(M^+ +1); ------

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 181), Masa (m/z): 493.19(M^+ +1); ------

(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Com-puesto Nro. 182), Masa (m/z): 496.17(M^+ +1); ----------

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 183), Masa (m/z): 498.15(M^+ +1); ----------

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Compuesto Nro. 184), Masa (m/z): 492.16 (M^+ +1); ---------

(2S,3R)-3-hidroxi-5-[4-(2-metoxipirimidin-5-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 185), Masa (m/z):476.13 (M^+ +1); ----------

(2S,3R) -5-[2-fluoro-4-(1-metil-1H-pirazol-4-il)fenil]-3-hi-droxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 186), Masa (m/z):480.08 (M^+ +1); ----------

(2S,3R)-5-[2-fluoro-4-(1-metil-1H-pirazol-4-il)fenil]-3-hi-droxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 187), Masa (m/z):480.15 (M^+ +1); ----------

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3 (4H)-il) e-til]-5-[2-fluoro-4-(1-metil-1H-pirazol-4-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 188), Masa (m/z):500.07 (M^+ +1); ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-5-[2-fluoro-4-(1-metil-1H-pirazol-4-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 189), Masa (m/z):500.13 (M^+ +1); ----------

(2S,3R)-5-[2-fluoro-4-(1-metil-1H-pirazol-4-il)fenil]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 190), Masa (m/z):484.15 (M^+ +1); ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[2-fluoro-4-(1-metil-1H-pirazol-4-il)fenil]-3-hi-droxi ácido pentanoico (Compuesto Nro. 191),

Masa (m/z):502.16 (M^+ +1); ----------

(2S,3R)-5-[2-fluoro-4-(1-metil-1H-pirazol-4-il)fenil]-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 192), Masa (m/z):507.22(M^+ +23); ----------

(2S,3R)-5-[2-fluoro-4-(1-metil-1H-pirazol-4-il)fenil]- 3-hi-droxi-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 193), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4-(2-metoxipirimidin-5-il)fenil]ácido pen-tanoico (Compuesto Nro. 194), Masa (m/z):506.12 (M^+ +1); ----

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-[4-(2-metoxipirimidin-5-il)fenil]ácido pentanoico (Compuesto Nro. 195), Masa (m/z):476.18 (M^+ +1); ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hi-droxi-2-[2-(1-oxoftalazin-2(1*H*)-il) etil] ácido pentanoico (Compuesto Nro. 196), Masa (m/z):465.26 (M^+ +1); ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hi-droxi-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il) etil]ácido pentanoico (Compuesto Nro. 197), Masa (m/z): 445.25 (M^+ +1); ----------

(2S,3R)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-{2-[4-oxo-7-(trifluorometil)-1,2,3-benzotriazin-3(4H)-il]etil}áci-do pentanoico (Compuesto Nro. 198), Masa (m/z): 543.22 (M^+ +1); ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(1-oxoftalazin-2(1*H*)-il)etil] ácido pentanoico (Compuesto Nro. 199), Masa (m/z):474.25(M^+ +1); ----------

(2S,3R)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2H) -il) etil] ácido pentanoico (Compuesto Nro. 200), Masa (m/z):454.24(M^+ +1); --

(2S,3R)-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-il) etil]-3-hi-droxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 201), Masa (m/z):495.27(M^+ +1); ----------

(2S,3R)-2-[2-(2,4-dioxo-2H-1,3-benzoxacin-3(4H)-il) etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 202), Masa (m/z):491.17(M^+ +1); ----------

(2S,3R)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(3, 4,4-trimetil-2,5-dioxoimidazolidin-1-il)etil]ácido pentanoi-co (Compuesto Nro. 203), Masa (m/z):470.12(M^+ +1); ----------

(2S,3R)-5-(4-cloro-3-fluorofenil)-2-[2-(1,3-dioxo-1,3-dihi-dro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico

(Com-puesto Nro. 204), Masa (m/z): 420.06 (M^+ +1); ----------

(2R,3S)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5 -(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 205), Masa (m/z): 476.07 (M^+ +1); ----------

(2R,3S)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5 -(4'-fluorobifenil-4-il)-3-hidroxi ácido pentanoico (Com-puesto Nro. 206), Masa (m/z):462.03 (M^+ +1); ----------

(2R,3S)-5-(3',4'-difluorobifenil-4-il)-2-[2- (1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 207), Masa (m/z):480.03 (M^+ +1); ----------

(2S,3S)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 208), Masa (m/z): 474.31 (M^+ +1); ----------

(2S,3R)-3-hidroxi-5-[4-(5-metilpiridin-2-il)fenil]- 2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 209), Masa (m/z): 459.21(M^+ +1); ----------

(2S,3R)-5-[4-(6-fluoropiridin-3-il)fenil]-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 210), Masa (m/z): 463.17(M^+ +1) ; ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il]ácido

pen-tanoico (Compuesto Nro. 211), Masa (m/z): 530.33(M^+ +1); ----

(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2- (7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 212), Masa (m/z): 492.29(M^+ +1); ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoi-co (Compuesto Nro. 213), Masa (m/z): 490.34 (M^+ +1); --------

(2*S*,3*R*)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Com-puesto Nro. 214), ----------

(2*S*,3*R*)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il) me-til]-5-[4'-(trifluorometil)bifenil-4-il]ácido pentanoico (Compuesto Nro. 215), Masa (m/z): 498.09 (M^+ +1); ----------

(2*S*,3*R*)-5-(2',4'-difluorobifenil-4-il)-3-hidroxi-2- [(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compues-to Nro. 216), Masa (m/z): 466.06 (M^+ +1); ----------

((2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3 -benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Compuesto Nro. 217), Masa (m/z): 448.07 (M^+ +1); ----------

(2*S*,3*R*)-5-(3'-fluoro-4'-metoxibifenil-4-il)-3-hidroxi-2-[(4 -oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico

(Compuesto Nro. 218), Masa (m/z): 478.22 (M^+ +1); ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(2-metoxipirimidin-5-il)fenil]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Com-puesto Nro. 219), Masa (m/z): 462.23 (M^+ +1); ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Com-puesto Nro. 220), Masa (m/z): 461.23 (M^+ +1); ----------

(2*S*,3*R*)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compuesto Nro. 221), Masa (m/z): 444.24 (M^+ +1); ----------

(2*S*,3*R*)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)me-til]-5-[4'-(trifluorometoxi)bifenil-4-il]ácido pentanoico (Compuesto Nro. 222), Masa (m/z): 514.14 (M^+ +1); ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]-2-[(4-oxo -1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Com-puesto Nro. 223), Masa (m/z): 445.18 (M^+ +1); ----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compuesto Nro. 224), Masa (m/z): 464.18 (M^+ +1); ----------

(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico

(Compues-to Nro. 225), Masa (m/z): 466.20 (M^+ +1); ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-hidroxipiridin-3-il)fenil] -2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 226), Masa (m/z): 461.23 (M^+ +1); ----------

(2*S*,3*R*)-3-hidroxi-5-(4'-metilbifenil-4-il)-2- {2- [4-oxo-7-(trifluorometil)-1,2,3-benzotriazin-3(4*H*)-il]etil}ácido pen-tanoico (Compuesto Nro. 227), Masa (m/z): 526.16 (M^+ +1); ---

(2*S*,3*R*)-2-[2-(2,4-dioxo-1,4-dihidroquinazolin-3(2*H*)-il)etil] -3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 228), Masa (m/z): 490.17 (M^+ +1) ----------

(2*S*,3*R*)-3-(acetiloxi)-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2 -(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 229), Masa (m/z): 517.06(M^+ +1); ----------

(2*S*,3*R*)-2-[2-(8-cloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) e-til]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido pen-tanoico (Compuesto Nro. 230) Masa (m/z): 509.17 (M^+ +1); ----

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-2-[2-(2,4-dioxo-2*H*-1,3-ben-zoxazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 231), Masa (m/z): 493.93 (M^+ +1) ----------

2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-(2-{[(2-hidroxi-fenil)carbonil]amino}etil) ácido pentanoico

(Compuesto Nro. 232), Masa (m/z): 468.14 (M^+ +1) ----------

Ejemplo: Ensayo para Proteinasas Metalo Matrices (MMPs). --

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Se prepararon nuevas entidades químicas del presente invento y los estándares correspondientes utilizados en el presente (inventario 10 mM) en 100% DMSO y se realizaron diluciones posteriores en 50% DMSO-50% TCNB (50 mM Tris, 10 mM $CaCl_2$, 150 mM NaCl, 0.05% Brij-35, pH 7.5). Se agregó 1 µl del compuesto y 88 µl de TCNB a recipientes de 96 bandejas recipiente para lograr la concentración final deseada de NCE (la concentración DMSO final no deberá exceder 0.5%). Se agregó 1 µl de MMPs activadas, recombinantes en cada recipiente (20-100 ng/100 µl de mezcla de la reacción) excepto en el "recipiente negativo". (Las enzimas MMP-1, 9 & 14 requieren activación anterior. Por eso, la enzima suministrada se incubó con APMA, concentración final 1 mM, durante un período de 1 hr a 37°C). Se realizó la incubación a temperatura ambiente durante 4-5 minutos. Se inició la reacción con 10 µl de 100 µM sustrato (ES001: las alícuotas se diluyeron vigorosamente en TCNB; inventario: 2 mM) y se monitoreó el aumento en la eflorescencia en longitud de onda de excitación de 320 nm seguida de la emisión a 405 nm durante 25-30 ciclos. Se calculó el aumento de la eflorescencia (RFU) como recipientes NCE/positivos, negativos y estándar. Se calculó el porcentaje de inhibición comparado con los

controles y los valores IC_{50} determinados utilizando el programa *Graph-prism*. ----------

El presente invento se relaciona con los compuestos que actúan como inhibidores de las MMP-9/12 duales, que tienen perfiles de actividasd deseados y potencia beneficiosa, selectividad y/o propiedades farmacocinéticas. ----------

En especial, los compuestos revelados en la presente exhiben actividad en los ensayos de la MMP9 de ≤ 0.02 nM hasta alrededor de 40 µM, o desde ≤ 0.02 nM hasta alrededor de 200 nM, o desde ≤ 0.02 nM hasta alrededor de 20 nM, o desde ≤ 0.02 nM hasta alrededor de 1.0 nM, o desde ≤ 0.02 nM hasta alrededor de 0.3 nM. Los compuestos revelados en la presente exhibieron actividad en ensayos de MMP12 desde ≤ 0.02 nM hasta alrededor de 3.8 µM, o desde ≤ 0.02 nM hasta alrededor de 200 nM, o desde ≤ 0.02 nM hasta alrededor de 20 nM, o desde ≤ 0.02 nM hasta alrededor de 1.0 nM, o desde ≤ 0.02 nM hasta alrededor de 0.3 nM. Los compuestos especiales analizados (Nros. 2-28, 30, 32-43, 46, 50-51, 55-58, 60-61, 63, 65-69, 76, 79-80, 86-89, 93-96, 98, 106-107, 113-122, 126, 130-132, 134, 136-138, 143-144, 148-150, 155, 157, 159, 173-175, 177, 179, 181-182, 184-186, 190, 192-195, 198 y 210-211) exhibieron actividad en ensayos de MMP1 desde alrededor de 100 nM hasta alrededor de 10 µM, por ejemplo desde alrededor de 100 nM hasta alrededor de 5 µM, o desde alrededor de 100 nM hasta alrededor de 2 µM, o desde alrededor de 100 nM hasta alrededor de 1 µM, indicando que los compuestos del

presente invento podrán ser selectivos sobre MMP-1 por ≥ 100 partes. ----------

Ensayo para modelo LPS inducido en neutrofilia de ratón *in vivo*. ----------

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Se trataron ratas *wistar* macho con vehículo / NCEs (nuevas entidades químicas) o droga estándar y 2 hrs después se estimularon con lipopolisacáridos (LPS) en fosfato amortiguado con solución salina (PBS), a través de la ruta intra-traqueal oronasal (400μL de 50μg/ml). Los animales de control negativo recibieron PBS solamente. Se realizó la instilación intratraqueal bajo quetamina y anestesia Xilazina. Dos horas después de la estimulación con LPS, se practicó eutanasia a las ratas y se llevó a cabo el lavaje broncoalveolar (BAL). Se realizó TLC, DLC para enumerar el recuento de neutrófilos en el fluido BAL y los resultados se expresaron como inhibición porcentual utilizando la siguiente fórmula ----------

-

$$\% \text{ Inhibición} = \frac{NeuLPS - NeuTEST}{NeuLPS - NeuPBS} \times 100$$

-

Donde, ----------

-

NeuLPS = recuento de neutrófilos en vehículo del grupo estimulado tratado con LPS. ----------

NeuTEST = recuento de neutrófilos en el grupo tratado con una dosis dada de un compuesto de análisis. ----------

NeuPBS = neutrófilos en vehículo del grupo estimulado trtado con PBS. ----------

Evaluación de Solubilidad. ----------

Solubilidad Equilibrada: ----------

El perfil de solubilidad del pH de un compuesto se determina a 37°C en medio acuoso con un pH en una escala de 1-7.5. Se evalúa una cantidad suficiente de condiciones del pH para definir en forma precisa el perfil de solubilidad del pH. Las soluciones amortiguadoras estándar descriptas en la USP se consideran apropiadas para uso en estudios de solubilidad. ----------

Se pesa el compuesto y se transfiere a los frascos. Se agregan los medios a cada frasco cónico, se sella el frasco con un tapón y película de parafina. El volumen agregado dependerá del volumen requerido para análisis del contenido del compuesto. El pH de la solución se mide después de agregar el compuesto. Se observa el frasco intermitentemente. Si la sustancia de la droga

está completamente disuelta, se agrega una cantidad adicional del compuesto hasta saturación (se observa el residuo no disuelto) y se mide el pH. Se sacan los frascos del baño de agua después que se logra el equilibrio. Se filtra la solución saturada a través de 0.45µm de filtro de membrana y se analizan las muestras para estimar el contenido del compuesto bajo análisis. ----------

Ensayos de investigación farmacocinética para los inhibidores de la Proteinasa Metalo Matriz (MMP 9/12). ----

Depuración intrínseca: ----------

Se evalúa la depuración intrínseca (o estabilidad del metabolismo) mediante estimación del índice de desintegración inicial del compuesto matriz en un modelo biológico adecuado como los microsomas del hígado humano. --

La reacción del estudio consiste en el sistema de regeneración NADPH y en los microsomas del hígado de las distintas especies de interés (seres humanos, ratas, perros, ratones), agregados al amortiguador a una concentración de 0.5 mg/mL. Después de una breve pre-incubación se inicia la reacción metabólica mediante el agregado de 5 µL del inventario de sustrato (100 µM) para producir una concentración final de 0.5 µM en la reacción. Las alícuotas periódicas se sacan cada tres minutos hasta 30 minutos, se templan y la concentración del compuesto del

análisis se estima por LCMS. El índice de desaparición se estima como la inclinación de primer orden del % matriz que permanece contra el gráfico de tiempo. El índice de desintegración se normaliza a la concentración unitaria del compuesto del análisis y proteína y se extrapola hasta 1g de hígado utilizando factores decisivos (52.5 mg de proteína microsómica CYP por gramo de hígado). ----------

Glucuronidación in vitro: ----------

Un ensayo comparativo en la forma de depuración intrínseca (ver supra) con el agregado de ácido glucurónico y alametacina para comparar primariamente la desaparición parental debido a la glucuronidación se expresa como índice de depuración y se normaliza por gramo de hígado. ---------

Unión de proteína plasma: ----------

Se estima evaluada por el método de diálisis equilibrada donde el compuesto no unido se esparce a través de una membrana semi-permeable y se equilibra con amortiguador fosfato (pH 7.4), y se sustrae del total de drogra en plasma para determinar el porcentaje unido. ----------

Las membranas de diálisis equilibradas se mojan durante la noche y se prepara el ensamble. Se inyecta la droga del análisis en plasma (100 y 1000 ng/mL) y se incuba a 37°C y se transfiere al aparato de equilibrio con plasma agregado

en un compartimiento y amortiguador en el otro. La unidad gira a rpm constante, a 37°C, durante cuatro horas para permitir que el compuesto no unido realice la diálisis y se distribuya en la cámara amortiguadora. Después de cuatro horas se saca el plasma y el amortiguador de los compartimientos respectivos y se estiman las concentraciones del compuesto del análisis. El porcentaje unido se estima de las concentraciones del compuesto del análisis. ----------

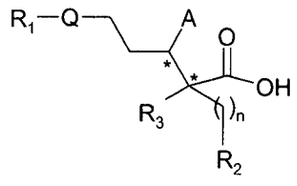
Los métodos alternativos incluyen el método de ultra filtración donde el compuesto inyectado en plasma (100 y 1000 ng/mL) se filtra con filtros Centricon (*Millipore*) teniendo corte de peso molecular de (30000 DA) para preparar el retenido y ultra filtrado. Se estima el compuesto del análisis en ambos y se calcula el porcentaje unido.---------

Reivindicaciones: ----------

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1. Un compuesto de la Fórmula I: ----------

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(I)

en donde: ----------

-

* representa un centro asimétrico estereogénico de configuración definida seleccionada de (R, R), (S, S), (R, S) y (S,R); ----------

-

n es un entero de 1 a 5; ----------

-

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

R_2 es heterociclilo, heteroarilo, NR_4R_5, $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$, $C(=Y)NR_4R_5$, $C(=O)OR_6$, --

--

en donde: ----------

Y es 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; ----------

--

R_x es R_4 o $-SO_2N(R_4)_2$; ----------

--

R_6 es hidrógeno, alquilo, cicloalquilo, aralquilo, heteroarilalquilo, heterociclilalquilo o cicloalquilalquilo en donde: ----------

-

R_4 es alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heterociclilo, heteroarilo, aralquilo, heteroarilalquilo, heterociclilalquilo o cicloalquilalquilo; y ----------

-

m es un entero 0-2; R_5 es hidrógeno o R_4; ----------

--

R_3 es hidrógeno, fluor, alquilo, cicloalquilalquilo o aralquilo; ----------

-

A es OH, OR_4, $-OC(=O)NR_4R_5$, O-acilo, NH_2, NR_4R_5, $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$; ----------

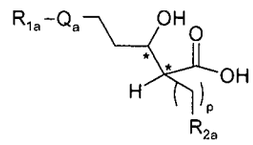
---

Q es arilo o heteroarilo opcionalmente sustituido. --------

-

2. Un compuesto de la Fórmula Ia ----------

-



(Ia)

en donde: ----------

-

* denota o representa un centro estereogénico o asimétrico de configuración definida seleccionado de (R, R), (S, S), (R, S) y (S,R); ----------

-

p es un entero de 1 a 3; ----------

-

R_{1a} es arilo o heteroarilo opcionalmente sustituido; ------

--

R_{2a} es N de 5-6 miembros que contiene heterociclilo unido a través del átomo N, que se fusiona opcionalmente al arilo, heteroarilo o se fusiona en espiral al cicloalquilo, que podrá ser también opcionalmente sustituido por uno o más del grupo oxo, alquilo, cicloalquilo, halo, alcoxi, trifluoroalquilo o arilo ----------

-

Q_a se encuentra opcionalmente sustituido con heteroarilo de 5 ó 6 miembros que contiene 1-4 heteroátomos seleccionados de O, N o S. ----------

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3. Un compuesto que se selecciona de: ----------

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(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-[6-(3-fluoro-4-metoxifenil)piridin-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 55), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[6-(4-metoxifenil)piridin-3-il]ácido pentanoico (Compuesto Nro. 57), ----------

(2*S*,3*R*)-5-[6-(4-clorofenil)piridin-3-il]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 59), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)ácido pentanoico (Compuesto Nro. 60), ----------

(2*S*,3*R*)-5-[4-(4-clorofenil)-2-tienil]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 61), ----------

(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)-2-tienil]ácido penta-noico (Compuesto Nro. 62), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-{4-[4-(trifluorometil)fenil]-2-tienil}ácido pen-tanoico (Compuesto Nro. 63), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-[4-(3-fluoro-4-metoxifenil)-2-tienil]-3-hidroxi ácido pentanoico (Compuesto Nro. 64), ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-{6-[4-(trifluorometil)fenil]piridin-3-il} ácido pentanoico (Compuesto Nro. 106), ----------

(2S,3R)-5-[6-(3,4-difluorofenil)piridin-3-il]-2-[2-(1,3-dio-xo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido penta-noico (Compuesto Nro. 107), ----------

(2S,3R)-5-[6-(4-cloro-3-fluorofenil)piridin-3-il]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 108), ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[6-(4-fluorofenil)piridin-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 109), ----------

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[6-(3-fluoro-4-metilfenil)piridin-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 110), ----------

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)ácido penta-noico (Compuesto Nro. 121), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)ácido penta-noico (Compuesto Nro. 122), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il) ácido pentanoico (Compuesto Nro. 123), ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il) ácido pen-tanoico (Compuesto Nro. 126), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-{6-[4-(trifluorometil)fenil] piridin-3-il} ácido pentanoico (Compuesto Nro. 130), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi-5-{6-[4-(trifluorometil)fenil]piridin-3-il} ácido pentanoico (Compuesto Nro. 131), ----------

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-{6-[4-(trifluorometil)fenil] piridin-3-il} ácido pentanoico (Compuesto Nro. 132), ----------

(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-{6-[4-(trifluorometil)fenil]piridin-3-il} áci-do pentanoico (Compuesto Nro. 133), ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)e-til]-3-hidroxi-5-{6-[4-(trifluorometil)fenil] piridin-3-il} ácido pentanoico (Compuesto Nro. 134), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 140), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoi-co (Compuesto Nro. 141), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoi-co (Compuesto Nro. 142), ----------

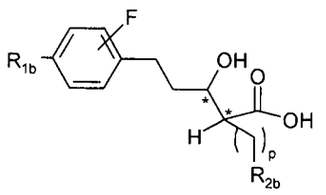
(2S,3R)-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)-2-tienil]-2 -[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 176), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 178), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoi-co (Compuesto Nro. 213), ----------

4. Un compuesto de la Fórmula Ib ----------

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(Ib)

en donde: ----------

-

* denota o representa un centro estereogénico o asimétrico de configuradición definida seleccionada de (R, R), (S, S), (R, S) y (S,R); ----------

-

p es un entero de 1 a 3; ----------

-

R_{1b} es feni o heteroarilo opcionalmente sustituido, en donde los sustituyentes opcionales se podrán seleccionar de entre uno o más de alquilo, cicloalquilo, halo, alcoxi, trifluoroalquilo o arilo; ----------

-

R_{2b} es N de 5-6 miembros que contiene heterociclilo unido a través del átomo N, que se fusiona opcionalmente al arilo, heteroarilo o al espiral fusionado al cicloalquilo, que podrá opcionalmente sustituirse también con uno o más de entre el grupo oxo, alquilo, halo, alcoxi, trifluoroalquilo o arilo.----------

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TOMO: 313

5. Un compuesto que se selecciona de: ----------

(2*S*,3*R*)-5-(3,3'-difluoro-4'-metoxibifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 47), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 50), ----------

(2*S*,3*R*)-5-(4'-cloro-3-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 56), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3-fluoro-4'-metoxibifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 58), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 153), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi-2-[2-(7-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 154), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 155), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 156), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 157), ----------

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3- hidroxi ácido pentanoico (Compuesto Nro. 163), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 164), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 165), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3- hidroxi ácido pentanoico (Compuesto Nro. 175), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 177), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3- hidroxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) etil] ácido pentanoico (Compuesto Nro. 186), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3- hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) etil] ácido pentanoico (Compuesto Nro. 187), ----------

(2*S*,3*R*)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) etil]-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 188), ----------

(2*S*,3*R*)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) etil]-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 189), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 190), ----------

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3 (4*H*)-il)etil]-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 191), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-2- [2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 192), ----------

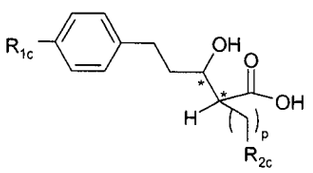
(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hidroxi-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 193), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3- hidroxi-2-[2-(1-oxoftalazin-2(1*H*)-il) etil] ácido pentanoico (Compuesto Nro. 196), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hidroxi-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il)etil]ácido pentanoico (Compuesto Nro. 197). ----------

6. Un compuesto de la Fórmula Ic ----------

-



(Ic)

en donde: ----------

-

* denota o representa un centro estereogénico o asimétrico de configuración definida seleccionada de (R, R), (S, S), (R, S) y (S,R); ----------

-

p es un entero de 1 a 3; ----------

-

R_{1c} es fenilo, piridilo, pirimidilo, tienilo o pirazolilo opcionalmentes sustituido; en donde el sustituyente opcional podrá seleccionarse de entre uno o más de alquilo, halo, alcoxi, trifluoroalquilo o arilo; ----------

---

R_{2c} es N de 5-6 miembros que contiene heterociclilo unido a través del átomo N, que se fusiona opcionalmente al arilo, heteroarilo o se fusiona en espiral al cicloalquilo, que podrá sustituirse opcionalmente también con uno o más de entre el grupo oxo, alquilo, cicloalquilo, halo, alcoxi, trifluoro alquilo o arilo.----------

-

7. Un compuesto que se selecciona de: ----------

-

(2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H) -il) etil]-5-(4-pirimidin-5-ilfenil)ácido pentanoico (Compuesto Nro.1), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro-2*H*- isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il) fenil] ácido pentanoico (Compuesto Nro. 2), ----------

(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]ácido pentanoico (Compuesto Nro. 3), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -(4'-fluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 4), ----------

(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-hidroxi ácido pentanoico (Compuesto Nro. 5), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 6), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3- dihidro- 2*H*-isoindol-2-il)etil]-5-[4-(6-metilpiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 7), ----------

(2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1, 3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]ácido pentanoico (Compuesto Nro. 8), ----------

(2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 9), ----------

(2*S*,3*R*)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 10), ----------

(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(5-me-til-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]ácido penta-noico (Compuesto Nro. 11), ----------

(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo -1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 12), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Com-puesto Nro. 13), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4'-(trifluorometoxi)bifenil-4-il]ácido pentanoi-co (Compuesto Nro. 14), ----------

(2*S*,3*R*)-5-(4'-cloro-3'-fluorobifenil-4-il)-3-hidroxi-2-[2-(4 -oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 15), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol -2-il)etil]-5-(3',4'-difluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 16), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol -2-il)etil]-3-hidroxi-5-(4'-metoxibifenil-4-il)ácido pen-tanoico (Compuesto Nro. 17), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4*H*)-il) etil]-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 18), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol -2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxi ácido pen-tanoico (Compuesto Nro. 19), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol -2-il)etil]-5-(4'-clorobifenil-4-il)-3-hidroxi ácido penta-noico (Compuesto Nro. 20), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4'-(trifluorometil)bifenil-4-il]ácido pentanoico (Compuesto Nro. 21), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)ácido pentanoico (Compuesto Nro. 22), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3'-fluoro-4'-metoxibifenil-4-il)-3-hidroxi ácido pentanoi-co (Compuesto Nro. 23), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]ácido pen-tanoico (Compuesto Nro. 24), ----------

(2*S*,3*R*)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 25), ----------

(2*S*,3*R*)-5-(4'-etilbifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 26), ----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil] ácido pentanoico (Compuesto Nro. 27), ----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 28), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4-pirimidin-5-ilfenil)ácido pentanoico (Compuesto Nro. 29), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]ácido pentanoi-co (Compuesto Nro. 30), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4-piridin-3-ilfenil)ácido pentanoico (Compuesto Nro. 31), ----------

(2*S*,3*R*)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil]-3-hi-droxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 32), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoi-co (Compuesto Nro. 33), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 34), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 35), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 36), ----------

(2*S*,3*R*)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 37), ----------

(2*S*,3*R*)-3-hidroxi-2-{2-[7-(6-metoxipiridin-3-il)-4-oxo-1,2,3 -benzotriazin-3(4*H*)-il]etil}-5-[4-(6-metoxipiridin-3-il) fe-nil]ácido pentanoico (Compuesto Nro. 38), ----------

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 39), ----------

(2*S*,3*R*)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) e-til]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 40), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 41), ----------

(2*S*,3*R*)-3-hidroxi-2-{2-[5-(6-metoxipiridin-3-il)-4-oxo-1,2,3 -benzotriazin-3(4*H*)-il]etil}-5-[4-(6-metoxipiridin-3-il) fe-nil]ácido pentanoico (Compuesto Nro. 42), ----------

(2*S*,3*R*)-5-(4'-cloro-3'-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoi-co Compuesto Nro. 43), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4-(1-isobutil-1*H*-pirazol-4-il)fenil]ácido penta-noico (Compuesto Nro. 44), ----------

(2*S*,3*R*)-5-bifenil-4-il-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoin-dol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 45), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 46), ----------

(2*S*,3*R*)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi áci-do pentanoico (Compuesto Nro. 48), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4-(1*H*-tetrazol-1-il)fenil]ácido pentanoico (Com-puesto Nro. 49), ----------

(2*S*,3*R*)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(4 -oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 51), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(1-isobutil-1*H*-pirazol-4-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 52), ----------

(2*S*,3*R*)-5-bifenil-4-il-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 53),

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoi-co (Compuesto Nro. 54), ----------

(2*S*,3*R*)-5-(4'-cloro-3-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 56), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido penta-noico (Compuesto Nro. 65), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido penta-noico (Compuesto Nro. 66), ----------

(2*S*,3*R*)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) e-til]-3-hidroxi-5-(4'-metilbifenil-4-il)ácido pentanoico (Compuesto Nro. 67), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido pen-

tanoico (Compuesto Nro. 68), ----------

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 69), ----------

(2*S*,3*R*)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) e-til]-3-hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Compuesto Nro. 76), ----------

(2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3 -benzotriazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 77), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4 *H*)-il)etil]-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]ácido pen-tanoico (Compuesto Nro. 78), ----------

(2*S*,3*R*)-2-[2-(5-cloro-1,3-dioxo-1,3-dihidro-2*H*- isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 79), ----------

(2*S*,3*R*)-2-[2-(4-fluoro-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 80), ----------

(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi ácido

pentanoico (Compuesto Nro. 81), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 *H*)-il)etil]-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]ácido penta-noico (Compuesto Nro. 90), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3 (4*H*)-il)etil]-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]ácido pen-tanoico (Compuesto Nro. 91), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-5-(3',4'-difluorobifenil-4-il)-3-hidroxi ácido penta-noico (Compuesto Nro. 92), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Compuesto Nro. 93), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-5-(4'-fluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 94), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 95), ----------

(2S,3R)-5-(2',4'-difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido

pentanoico (Compuesto Nro. 97), ----------

(2S,3R)-2-[2-(6-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 98), ----------

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(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 99), ----------

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(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-(4'-isopropilbifenil-4-il)ácido pentanoico (Com-puesto Nro. 100), ----------

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(2S,3R)-5-(3'-cloro-4'-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoi-co (Compuesto Nro. 101), ----------

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(2S,3R)-5-(4'-butilbifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3 -benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 102), ----------

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(2S,3R)-5-(2'-fluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 103), ----------

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(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido

pentanoico (Compuesto Nro. 104), ----------

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(2S,3R)-3-hidroxi-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pen-tanoico (Compuesto Nro. 105), ----------

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(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 111), ----------

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(2S,3R)-2-[2-(8-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido pentanoico (Compuesto Nro. 112), ----------

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(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin- 3(4H)-il)etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] áci-do pentanoico (Compuesto Nro. 113), ---------

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(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-[4'-(trifluorometoxi)bifenil-4-il] ácido pen-tanoico (Compuesto Nro. 114), ----------

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(2S,3R)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 115), ----------

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(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico

(Com-puesto Nro. 116), ----------

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(7-me-til-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 117), ----------

(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 118), ----------

(2S,3R)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil]-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 119), ----------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(7 -metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 124), ----------

(2S,3R)-3-hidroxi-5-[4-(1-isobutil-1H-pirazol-4-il)fenil]-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 125), ----------

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(8-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 127), ----------

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(8-me-toxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido

pentanoico (Compuesto Nro. 128), ----------

(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 129), ----------

(2S,3R)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-(4'-metilbifenil-4-il)ácido pentanoico (Com-puesto Nro. 135), ----------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido penta-noico (Compuesto Nro. 136), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)ácido pentanoico (Compuesto Nro. 137), ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)e-til]-3-hidroxi-5-(4'-metilbifenil-4-il)ácido pentanoico (Compuesto Nro. 138), ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 139), ----------

(2*S*,3*S*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico

(Com-puesto Nro. 143), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 144), ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(6,7-difluoro-4-oxo-1, 2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 145), ----------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(8 -metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 146), ----------

(2S,3R)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil]- 3-hi-droxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 147), ----------

(2S,3R)-5-[4-(6-cloropiridin-3-il)fenil]-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 148), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il] ácido pen-tanoico (Compuesto Nro. 149), ----------

(2S,3R)-3-hidroxi-2-[2-(7-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido

pen-tanoico (Compuesto Nro. 150), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-(4'-metilbifenil-4-il)ácido pentanoico (Com-puesto Nro. 151), ----------

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(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(6-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 152), ----------

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(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(7-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 158), ----------

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(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 159), ----------

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(2S,3R)-3-hidroxi-2-[2-(7-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4-(6-metoxipiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 160), ----------

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(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(7-me-toxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 161), ----------

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(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4-(6-metoxipiridin-3-il)fenil]ácido penta-

noico (Compuesto Nro. 162), ----------

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(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 166), ----------

(2S,3R)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoi-co (Compuesto Nro. 167), ----------

(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 168), ----------

(2S,3R)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 169), ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 170), ----------

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(6-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 171), ----------

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(6-me-toxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido

pentanoico (Compuesto Nro. 172), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4'-(trifluorometoxi)bifenil-4-il]ácido pen-tanoico (Compuesto Nro. 173), ----------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(6 -metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 174), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 179), ----------

(2S,3R)-5-[4-(2-cloropiridin-3-il)fenil]-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 180), ----------

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil] ácido pen-tanoico (Compuesto Nro. 181), ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Com-puesto Nro. 182), ----------

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido

pentanoico (Compuesto Nro. 183), ----------

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)e-til]-3-hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Compuesto Nro. 184), ----------

-

(2*S*,3*R*)-3-hidroxi-5-[4-(2-metoxipirimidin-5-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 185), ----------

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(2*S*,3*R*)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4*H*)-il)etil]-5-[4-(2-metoxipirimidin-5-il)fenil]ácido pen-tanoico (Compuesto Nro. 194), ----------

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(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4-(2-metoxipirimidin-5-il)fenil]ácido pentanoico (Compuesto Nro. 195), ----------

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(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-{2-[4-oxo-7-(trifluorometil)-1,2,3-benzotriazin-3(4*H*)-il]etil}áci-do pentanoico (Compuesto Nro. 198), ----------

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(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(1-oxoftalazin-2(1*H*)-il)etil]ácido pentanoico (Compuesto Nro. 199)----------

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(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il)etil]

ácido pentanoico (Compuesto Nro. 200), ----------

(2*S*,3*R*)-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-il)etil]-3-hi-droxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 201), ----------

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(2*S*,3*R*)-2-[2-(2,4-dioxo-2*H*-1,3-benzoxazin-3(4*H*)-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 202), ----------

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(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(3, 4,4-trimetil-2,5-dioxoimidazolidin-1-il)etil]ácido pentanoi-co (Compuesto Nro. 203), ----------

---

(2S,3R)-5-(4-cloro-3-fluorofenil)-2-[2-(1,3-dioxo-1,3-dihi-dro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 204), ----------

-

(2R,3S)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5 -(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 205), ----------

---

(2*R*,3*S*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -(4'-fluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 206), ----------

-

(2*R*,3*S*)-5-(3',4'-difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido

pentanoico (Compuesto Nro. 207), ----------

(2*S*,3*S*)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 208), ----------

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(2*S*,3*R*)-3-hidroxi-5-[4-(5-metilpiridin-2-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 209), ----------

---

(2*S*,3*R*)-5-[4-(6-fluoropiridin-3-il)fenil]-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 210), ----------

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(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il]ácido pen-tanoico (Compuesto Nro. 211), ----------

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(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 212), ----------

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(2*S*,3*R*)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Com-puesto Nro. 214), ----------

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(2*S*,3*R*)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il) me-til]-5-[4'-(trifluorometil)bifenil-4-il]ácido pentanoico

(Compuesto Nro. 215), ----------

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(2*S*,3*R*)-5-(2',4'-difluorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Com-puesto Nro. 216), ----------

---

((2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3 -benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compuesto Nro. 217), ----------

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(2*S*,3*R*)-5-(3'-fluoro-4'-metoxibifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Com-puesto Nro. 218), ----------

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(2*S*,3*R*)-3-hidroxi-5-[4-(2-metoxipirimidin-5-il)fenil]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Com-puesto Nro. 219), ----------

---

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2- [(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Com-puesto Nro. 220), ----------

---

(2*S*,3*R*)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compuesto Nro. 221), ----------

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(2*S*,3*R*)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il) me-til]-5-[4'-(trifluorometoxi)bifenil-4-il] ácido

pentanoico (Compuesto Nro. 222), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]-2-[(4-oxo -1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Com-puesto Nro. 223), ----------

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(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil] ácido pentanoico (Compuesto Nro. 224), ----------

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(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compues-to Nro. 225), ----------

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(2*S*,3*R*)-3-hidroxi-5-[4-(6-hidroxipiridin-3-il)fenil]-2-[2-(4 -oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 226), ----------

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(2*S*,3*R*)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-{2-[4- oxo -7-(trifluorometil)-1,2,3-benzotriazin-3(4*H*)-il]etil}ácido pen-tanoico (Compuesto Nro. 227), ----------

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(2*S*,3*R*)-2-[2-(2,4-dioxo-1,4-dihidroquinazolin-3(2*H*)-il)etil] -3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 228), ----------

---

(2*S*,3*R*)-2-[2-(8-cloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) e-til]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido

penta-noico Compuesto Nro. 230), ----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-2-[2-(2,4-dioxo-2*H*-1,3-ben-zoxazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 231). ----------

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8. Un compuesto que se selecciona de: ----------

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(2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil]-5-fenil ácido pentanoico (Compuesto Nro. 82), ----

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-fenil ácido pentanoico (Compuesto Nro. 83), ---

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4(trifluorometil)fenil] ácido pentanoico (Com-puesto Nro. 84), ----------

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(2*S*,3*R*)-5-(4-*tert*-butilfenil)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro.85), ----------

-

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -[2-fluoro-5-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 70), ----------

-

(2*S*,3*R*)-5-(4'-cloro-4-fluorobifenil-3-il)-2-[2-(1,3-dioxo-1, 3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 71), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -[6-fluoro-4'-(trifluorometil)bifenil0-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 72), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -[4-fluoro-3-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 73), ----------

(2*S*,3*R*)-5-(4'-cloro-6-fluorobifenil-3-il)-2-[2-(1,3-dioxo-1, 3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 74), ----------

(2*S*,3*R*)-5-(3',6-difluoro-4'-metoxibifenil-3-il)-2-[2- (1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 75), ----------

(2*S*,3*R*)-3-(acetiloxi)-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2 -(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 229), ----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-(2-{[(2-hidroxi fenil)carbonil]amino}etil) ácido pentanoico (Compuesto Nro. 232). ----------

9. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 y, junto con los conductores farmacéuticamente aceptables, los excipientes o diluyentes.

10. La composición farmacéutica de la reivindicación 9 que comprende además uno o más ingredientes activos adicionales seleccionados del grupo que consiste de: ----------

a. Agentes anti-inflamatorios, seleccionados de (i) los agentes anti-inflamatorios no esteroidales piroxicam, diclofenac, ácidos propiónico, fenamatos, pirazolonas, salicilatos, Inhibidores de PDE-4/p38 MAP Quinasa/Catepsina, antagonistas CCR-3, inhibidores iNOS, inhibidores de triptasa y elastasa, antagonistas de integrina beta-2, inhibidores de adhesión celular, y agonistas de la adenosina 2a (ii) Inhibidores de leucotrienos LTC4/LTD4/LTE4/LTB4-, inhibidores de 5-lipoxigenasa y antagonistas receptores PAF, (iii) Inhibidores de Cox-2; (iv) otros inhibidores de la MMP; (v) inhibidores de interleuquina-I; (vi) los corticoesteroides alclometasona, amcinonida, amelometasona, beclometasona, betametasona, budesonida, ciclesonida, clobetasol, cloticasona, ciclometasona, deflazacort, deprodona, dexbudesonida, diflorasona, difluprednato, fluticasona, flunisolida, halometasona, halopredona, hidrocortisona, hidrocortisona, metilprednisolona, mometasona, prednicarbato, prednisolona, rimexolona, tixocortol, triamcinolona, ulobetasol, rofleponida, GW 215864, KSR 592, ST-126, dexametasona y las sales, solvatos

farmacéuticamente aceptables de los mismos; ----------
-

b) agonistas Beta, seleccionados de los agonistas β2 albuterol, salbutamol, biltolterol, pirbuterol, levosalbutamol, tulobuterol, terbutalina, bambuterol, metaproterenol, fenoterol, salmeterol, carmoterol, arformoterol, formoterol, y las sales o solvatos farmacéuticamente aceptables de los mismos; ----------
-

c) agentes antihipertensivos seleccionados de (i) los inhibidores ACE, enalapril, lisinopril, valsartan, telmisartan y quinapril, (ii) los agonistas receptores de angiotensina II y los agonistas losartan, candesartan, irbesartan, valsartan, y eprosartan, (iii) β-bloqueantes, y (iv) bloqueadores del canal de calcio; ----------
-

Con formato: Numeración y viñetas

d) agentes inmunosupresores seleccionados de ciclosporina, azatioprina y metotrexato, corticoesteroides anti-inflamatorios; y ----------
-

e) los agentes anti-infecciosos, antibióticos y antivirales.

11. Un método para el tratamiento o profilaxis de un animal o ser humano que sufre de una enfermedad inflamatoria o desorden de autoinmunidad que comprende la administración al animal o ser humano de una cantidad efectiva de un compuesto de acuerdo con la reivindicación 1-8. ----------

12. Un método para el tratamiento o profilaxis de un amimal o ser humano que sufre de una enfermedad inflamatoria o desorden de autoinmunidad que comprende la administración al animal o ser humano de una cantidad efectiva de la composición farmacéutica de acuerdo con la reivindicación 9.

13. Un método para el tratamiento de o profilaxis de un animal o un ser humano que sufre de una enfermedad inflamatoria o desorden de autoinmunidad que comprende la administración al animal o al ser humano de una cantidad efectiva de la composición farmacéutica de acuerdo con la reivindicación 10. ----------

14. Un auxiliar quiral que es (4S)-4-bencil-1,3-tiazolidin-2-ona. ----------

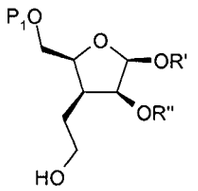
15. Uso de un auxiliar quiral de la reivindicación 14 en reacciones de transformación química sintética seleccionado de condensación asimétrica de aldol, alquilación estereoselectiva, reacción de *Diels-Alder* estereoselectiva, reaccones de *Michael* estereoselectiva, reacciones de diferenciación estereoselectivas de grupos enantiotópicos en moléculas que llevan centros pro-quirales. ----------

16. Un proceso para preparer un compuesto de la Fórmula XX que comprende: ----------

a) reaccionar un compuesto de la Fórmula VIIIa ----------

Con formato: Numeración y viñetas

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Formula VIIIa

Con un compuesto de la Fórmula IX ----------

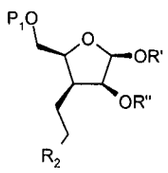
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R_2-H

Formula IX

para dar un compuesto de la Fórmula X; ----------

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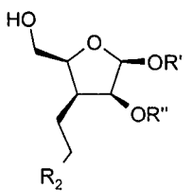


Formula X

b) desproteger el compuesto de la Fórmula X para dar un compuesto de la Fórmula XI; ----------

Con formato: Numeración y viñetas

-

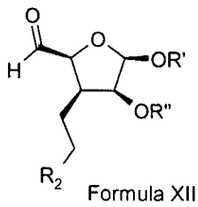


Formula XI

c) oxidizar el compuesto de la Fórmula XI para dar un compuesto de la Fórmula XII; ----------

Con formato: Numeración y viñetas

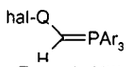
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Formula XII

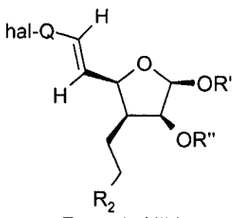
d) reaccionar el compuesto de la Fórmula XII con un compuesto de la Fórmula XIII ----------

Con formato: Numeración y viñetas



Formula XIII

para dar un compuesto de la Fórmula XIV; ----------



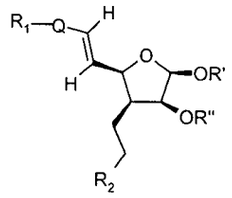
Formula XIV

e) reaccionar el compuesto de la Fórmula XIV con un compuesto de la Fórmula XV ----------

Con formato: Numeración y viñetas

R_1-$B(OH)_2$
Formula XV

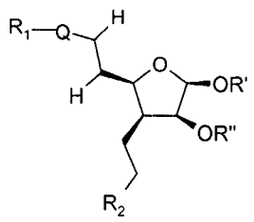
Para dar un compuesto de la Fórmula XVI; ----------



Formula XVI

f) hidrogenar un compuesto de la Fórmula XVI para dar un compuesto de la Fórmula XVII ----------

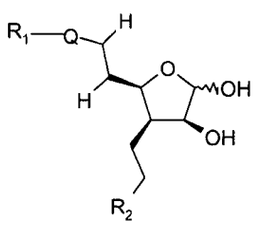
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Formula XVII

g) desproteger el compuesto de la Fórmula XVII para dar un compuesto de la Fórmula XVIII; ----------

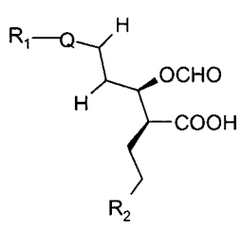
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Formula XVIII

h) convertir el compuesto de la Fórmula XVIII en un compuesto de la Fórmula XIX; y ----------

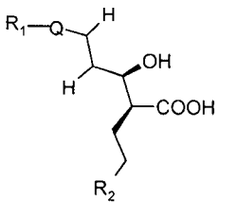
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Formula XIX

i) desformilar el compuesto de la Fórmula XIX para dar el compuesto de la Fórmula XX. ----------

Con formato: Numeración y viñetas



Formula XX

en donde: ----------

P_1 es un grupo protector sililo; ----------

R' y R" juntos forman un grupo protector acetal; ----------

R_2 es un heterociclilo o heteroarilo que contiene N; ----------

hal es Cl, Br o I; ----------

Ar es fenilo; ----------

Q es arilo o heteroarilo opcionalmente sustituido; y ----------

R_1 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heterociclilo, heteroarilo, aralquilo, alcoxi, ariloxi, alqueniloxy o alquiniloxi opcionalmente sustituidos. ----------

17. El proceso de acuerdo con la reivindicación 16, en donde los compuestos de la Fórmula XX se seleccionan de: ---

(2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil]-5-(4-pirimidin-5-ilfenil)ácido pentanoico (Compuesto Nro.1), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol -2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 2), ----------

(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]ácido pentanoico (Compuesto Nro. 3), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -(4'-fluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 4), ----------

(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-hidroxi ácido pentanoico (Compuesto No. 5), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 6), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3- dihidro -2*H*-isoindol-2-il)etil]-5-[4-(6-metilpiridin-3-il)fenil] ácido pentanoico (Compuesto Nro. 7), ----------

(2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1, 3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]ácido pentanoico (Compuesto Nro. 8), ----------

(2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 9), ----------

(2*S*,3*R*)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 10), ----------

(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(5-me-til-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]ácido penta-noico (Compuesto Nro. 11), ----------

(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo -1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compues-to Nro. 12), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Compues-to Nro. 13), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometoxi)bifenil-4-il]ácido pentanoi-co (Compuesto Nro. 14), ----------

(2*S*,3*R*)-5-(4'-cloro-3'-fluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 15), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3',4'-difluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 16), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metoxibifenil-4-il) ácido penta-noico (Compuesto Nro. 17), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido pentanoico (Compuesto Nro. 18), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxi ácido pen-tanoico (Compuesto Nro. 19), ----------

(2*S*,3*R*)-2-[2-(5-*tert*-butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-clorobifenil-4-il)-3-hidroxi ácido penta-noico (Compuseto Nro. 20), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoi-co (Compuesto Nro. 21), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)ácido pentanoico (Compuesto Nro. 22), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3'-fluoro-4'-metoxibifenil-4-il)-3-hidroxi ácido pentanoi-co (Compuesto Nro. 23), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]ácido pen-tanoico (Compuesto Nro. 24), ----------

(2*S*,3*R*)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 25), ----------

(2*S*,3*R*)-5-(4'-etilbifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 26), ----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1, 3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]ácido pentanoico (Compuesto Nro. 27), ----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 28), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4-pirimidin-5-ilfenil)ácido pentanoico (Compues-to Nro. 29), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]ácido pentanoi-co (Compuesto Nro. 30), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4-piridin-3-ilfenil)ácido pentanoico (Compuesto Nro. 31), ----------

(2*S*,3*R*)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil]-3-hi-droxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil] ácido pentanoico (Compuesto Nro. 32), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoi-co (Compuesto Nro. 33), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 34), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 35), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro. 36), ----------

(2*S*,3*R*)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 37), ----------

(2*S*,3*R*)-3-hidroxi-2-{2-[7-(6-metoxipiridin-3-il)-4-oxo-1,2,3 -benzotriazin-3(4*H*)-il]etil}-5-[4-(6-metoxipiridin-3-il) fe-nil] ácido pentanoico (Compuesto Nro. 38), ----------

2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin- 3 (4*H*)-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il) fenil] ácido pentanoico (Compuesto Nro. 39), ----------

(2*S*,3*R*)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) e-til]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 40), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3 (4*H*)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 41), ----------

(2*S*,3*R*)-3-hidroxi-2-{2-[5-(6-metoxipiridin-3-il)-4-oxo-1, 2, 3-benzotriazin-3(4*H*)-il]etil}-5-[4-(6-metoxipiridin- 3-il) fenil]ácido pentanoico (Compuesto Nro. 42), ----------

(2*S*,3*R*)-5-(4'-cloro-3'-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoi-co (Compuesto Nro. 43), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4-(1-isobutil-1*H*-pirazol-4-il)fenil]ácido penta-noico (Compuesto Nro. 44), ----------

(2*S*,3*R*)-5-bifenil-4-il-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoin-dol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 45), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 46), ----------

(2*S*,3*R*)-5-(3,3'-difluoro-4'-metoxibifenil-4-il)-2-[2- (1, 3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 47), ----------

(2*S*,3*R*)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi áci-do pentanoico (Compuesto Nro. 48), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4-(1*H*-tetrazol-1-il)fenil]ácido pentanoico (Com-puesto Nro. 49), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 50), ----------

(2*S*,3*R*)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(4 -oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 51), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(1-isobutil-1*H*-pirazol-4-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 52), ----------

(2*S*,3*R*)-5-bifenil-4-il-3-hidroxi-2-[2-(4-oxo-1,2,3- benzo-triazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 53),

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoi-co (Compuesto Nro. 54), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -[6-(3-fluoro-4-metoxifenil)piridin-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 55), ----------

(2*S*,3*R*)-5-(4'-cloro-3-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1, 3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido

pentanoico (Compuesto Nro. 56), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[6-(4-metoxifenil)piridin-3-il]ácido pentanoico (Compuesto Nro. 57), ----------

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(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3-fluoro-4'-metoxibifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 58), ----------

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(2*S*,3*R*)-5-[6-(4-clorofenil)piridin-3-il]-2-[2-(1,3-dioxo-1, 3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 59), ----------

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(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)ácido pentanoico (Compuesto Nro. 60), ----------

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(2*S*,3*R*)-5-[4-(4-clorofenil)-2-tienil]-2-[2-(1,3-dioxo- 1, 3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 61), ----------

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(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)-2-tienil]ácido penta-noico (Compuesto Nro. 62), ----------

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(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-{4-[4-(trifluorometil)fenil]-2-tienil}ácido

pen-tanoico (Compuesto Nro. 63), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-[4-(3-fluoro-4-metoxifenil)-2-tienil]-3-hidroxi ácido pen-tanoico (Compuesto Nro. 64), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido penta-noico (Compuesto Nro. 65), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido penta-noico (Compuesto Nro. 66), ----------

(2*S*,3*R*)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) etil]-3-hidroxi-5-(4'-metilbifenil-4-il)ácido pentanoico (Compuesto Nro. 67), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido pentanoico (Compuesto Nro. 68), ----------

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] pen-tanoico (Compuesto Nro. 69), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-[2-fluoro-5-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido

pentanoico (Compuesto Nro. 70), ----------

(2*S*,3*R*)-5-(4'-cloro-4-fluorobifenil-3-il)-2-[2-(1,3-dioxo-1, 3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 71), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -[6-fluoro-4'-(trifluorometil)bifenil-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 72), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5 -[4-fluoro-3-(6-metoxipiridin-3-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro. 73), ----------

(2*S*,3*R*)-5-(4'-cloro-6-fluorobifenil-3-il)-2-[2-(1,3-dioxo-1, 3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 74), ----------

(2*S*,3*R*)-5-(3',6-difluoro-4'-metoxibifenil-3-il)-2-[2- (1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 75), ----------

(2*S*,3*R*)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) e-til]-3-hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Compuesto Nro. 76), ----------

(2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3 -benzotriazin-3(4*H*)-il)etil]-3-hidroxi ácido

pentanoico (Compuesto Nro. 77), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4 *H*)-il)etil]-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]ácido penta-noico (Compuesto Nro. 78), ----------

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(2*S*,3*R*)-2-[2-(5-cloro-1,3-dioxo-1,3-dihidro-2*H*-isoindol- 2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 79), ----------

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(2*S*,3*R*)-2-[2-(4-fluoro-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il] ácido pentanoico (Compuesto Nro. 80), ----------

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(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 81), ----------

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(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 86), ----------

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(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro -2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 87), ----------

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(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]ácido

pentanoico (Compuesto Nro.88), ----------

(2*S*,3*R*)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 *H*)-il)etil]-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]ácido penta-noico (Compuesto Nro. 90), ----------

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(2*S*,3*R*)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(1-metil-1*H*-pirazol-4-il)fenil]ácido pen-tanoico (Compuesto Nro. 91), ----------

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(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-5-(3',4'-difluorobifenil-4-il)-3-hidroxi ácido penta-noico (Compuesto Nro. 92), ----------

-

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Compuesto Nro. 93), ----------

-

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-5-(4'-fluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 94), ----------

-

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 95), ----------

-

(2S,3R)-5-(2',4'-difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico

(Compuesto Nro. 97), ----------

-

(2S,3R)-2-[2-(6-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il) fenil]ácido pentanoico (Compuesto Nro. 98), ----------

-

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il) fenil] pentanoico (Compuesto Nro. 99), ----------

-

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-(4'-isopropilbifenil-4-il)ácido pentanoico (Com-puesto Nro. 100), ----------

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(2S,3R)-5-(3'-cloro-4'-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoi-co Compuesto Nro. 101), ----------

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(2S,3R)-5-(4'-butilbifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3 -benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 102), ----------

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(2S,3R)-5-(2'-fluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 103), ----------

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(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)fenil] ácido

pentanoico (Compuesto Nro. 104), ----------

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(2S,3R)-3-hidroxi-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-[4-(1-metil-1H-pirazol-4-il)fenil]ácido penta-noico (Compuesto Nro. 105), ----------

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(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3 -hidroxi-5-{6-[4-(trifluorometil)fenil]piridin-3-il} ácido pentanoico (Compuesto Nro. 106), ----------

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(2S,3R)-5-[6-(3,4-difluorofenil)piridin-3-il]-2-[2-(1,3-dio-xo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido penta-noico (Compuesto Nro. 107), ----------

---

(2S,3R)-5-[6-(4-cloro-3-fluorofenil)piridin-3-il]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 108), ----------

---

(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5 -[6-(4-fluorofenil)piridin-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 109), ----------

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(2S,3R)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5 -[6-(3-fluoro-4-metilfenil)piridin-3-il]-3-hidroxi ácido pentanoico (Compuesto Nro. 110), ----------

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(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il) fenil] ácido

pentanoico (Compuesto Nro. 111), ----------
-

(2S,3R)-2-[2-(8-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il) fenil] ácido pentanoico (Compuesto Nro. 112), ----------
-

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il) fenil] ácido pentanoico (Compuesto Nro. 113), ----------
----

(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-[4'-(trifluorometoxi)bifenil-4-il]ácido pen-tanoico (Compuesto Nro. 114), ----------
-----

(2S,3R)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 115), ----------
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(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 116), ----------
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(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(7-me-til-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 117), ----------
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(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil]ácido

pentanoico (Compuesto Nro. 118), ----------

(2S,3R)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil]-3-hi-droxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil] ácido pentanoico (Compuesto Nro. 119), ----------

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)ácido penta-noico (Compuesto Nro. 121), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)ácido penta-noico (Compuesto Nro. 122), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il) ácido pentanoico (Compuesto Nro. 123), ----------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(7 -metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 124), ----------

(2S,3R)-3-hidroxi-5-[4-(1-isobutil-1H-pirazol-4-il)fenil]-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 125), ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)ácido

penta-noico Compuesto Nro. 126), ----------

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(8-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 127), ----------

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(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(8-me-toxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 128), ----------

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(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(8-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 129), ----------

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(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-{6-[4-(trifluorometil)fenil]piridin-3- il} ácido pentanoico (Compuesto Nro. 130), ----------

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(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin- 3 (4H)-il)etil]-3-hidroxi-5-{6-[4-(trifluorometil)fenil]piridin- 3-il}ácido pentanoico (Compuesto Nro. 131), ----------

(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-{6-[4-(trifluorometil)fenil]piridin-3- il} ácido pentanoico (Compuesto Nro. 132), ----------

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(2S,3R)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4 H)-il)etil]-5-{6-[4-(trifluorometil)fenil]piridin-3-il}

áci-do pentanoico (Compuesto Nro. 133), ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-{6-[4-(trifluorometil)fenil]piridin- 3-il} ácido pentanoico (Compuesto Nro. 134), ----------

(2S,3R)-3-hidroxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-(4'-metilbifenil-4-il)ácido pentanoico (Com-puesto Nro. 135), ----------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido penta-noico (Compuesto Nro. 136), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin- 3 (4H)-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)ácido pentanoico (Compuesto Nro. 137), ----------

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(4'-metilbifenil-4-il)ácido pentanoico (Compuesto Nro. 138), ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Com-puesto Nro. 139), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico

(Com-puesto Nro. 140), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoi-co (Compuesto Nro. 141), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoi-co (Compuesto Nro. 142), ----------

(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro. 144), ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(6,7-difluoro-4-oxo-1, 2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 145), ----------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(8 -metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 146), ----------

(2S,3R)-5-[4-(2,3-dihidro-1,4-benzodioxin-6-il)fenil]-3-hi-droxi-2-[2-(8-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 147), ----------

(2S,3R)-5-[4-(6-cloropiridin-3-il)fenil]-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico

(Com-puesto Nro. 148), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido pentanoico (Compuesto Nro. 149), ----------

(2S,3R)-3-hidroxi-2-[2-(7-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]ácido pen-tanoico (Compuesto Nro. 150), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3 (4H)-il)etil]-5-(4'-metilbifenil-4-il)ácido pentanoico (Com-puesto Nro. 151), ----------

(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(6-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 152), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidro-xi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 153), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(7-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro. 154), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]- 3-

hidroxi ácido pentanoico (Compuesto Nro. 155), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 156), ----------

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(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro. 157), ----------

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(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(7-metoxi-4 -oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 158), ----------

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(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro. 159), ----------

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(2S,3R)-3-hidroxi-2-[2-(7-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro.160), ----------

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(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(7-me-toxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro.161), ----------

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(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4-(6-metoxipiridin-3-il)fenil]ácido penta-

noico (Compuesto Nro.162), ----------

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(2S,3R)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) etil]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]- 3- hidroxi ácido pentanoico (Compuesto Nro.163), ----------

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(2S,3R)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidro-xi ácido pentanoico (Compuesto Nro.164), ----------

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(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil] ácido pentanoico (Compuesto Nro.165), ----------

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(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro.166), ----------

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(2S,3R)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoi-co (Compuesto Nro.167), ----------

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(2S,3R)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro.168), ----------

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(2S,3R)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico

(Com-puesto Nro.169), ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro.170), ----------

(2S,3R)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro.171), ----------

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[2-(6-me-toxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro.172), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4'-(trifluorometoxi)bifenil-4-il]ácido pen-tanoico (Compuesto Nro. 173), ----------

(2S,3R)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro.174), ----------

(2S,3R)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3- hidroxi ácido pentanoico (Compuesto Nro.175), ----------

(2S,3R)-3-hidroxi-5-[4-(1-metil-1H-pirazol-4-il)-2-tienil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido

pentanoico (Compuesto Nro. 176), ----------

(2S,3R)-5-[2-fluoro-4-(6-metoxipiridin-3-il)fenil]-3-hidroxi -2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Compuesto Nro.177), ----------

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 178), ----------

(2S,3R)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4-(6-metilpiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 179), ----------

(2S,3R)-5-[4-(2-cloropiridin-3-il)fenil]-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido penta-noico (Compuesto Nro. 180), ----------

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido penta-noico (Compuesto Nro. 181), ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido pentanoico (Com-puesto Nro.182), ----------

(2S,3R)-5-(3',4'-difluorobifenil-4-il)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-3-hidroxi ácido

pentanoico (Compuesto Nro. 183), ----------

(2S,3R)-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-(4'-metoxibifenil-4-il)ácido pentanoico (Compuesto Nro.184), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(2-metoxipirimidin-5-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro.185), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hi-droxi-2-[2-(6-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) etil] ácido pentanoico (Compuesto Nro.186), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hi-droxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) etil] ácido pentanoico (Compuesto Nro.187), ----------

(2*S*,3*R*)-2-[2-(5-cloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) e-til]-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro.188), ----------

(2*S*,3*R*)-2-[2-(7-cloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) e-til]-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hidroxi ácido pentanoico (Compuesto Nro.189), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-

hidroxi ácido pentanoico (Compuesto Nro.190), ----------

(2*S*,3*R*)-2-[2-(6,7-difluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hi-droxi ácido pentanoico (Compuesto Nro. 191), ----------

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-2-[2-(6-fluoro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro.192), ----------

---

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hi-droxi-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) etil] ácido pentanoico (Compuesto Nro.193), ----------

---

(2*S*,3*R*)-3-hidroxi-2-[2-(6-metoxi-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4-(2-metoxipirimidin-5-il)fenil]ácido pentanoico (Compuesto Nro.194), ----------

-

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4-(2-metoxipirimidin-5-il)fenil]ácido pentanoico (Compuesto Nro.195), ----------

---

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hi-droxi-2-[2-(1-oxoftalazin-2(1*H*)-il) etil]ácido pentanoico (Compuesto Nro.196), ----------

---

(2*S*,3*R*)-5-[2-fluoro-4-(1-metil-1*H*-pirazol-4-il)fenil]-3-hi-droxi-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-

1(2*H*)-il) etil]ácido pentanoico (Compuesto Nro.197), ------

---

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-{2-[4-oxo-7-(trifluorometil)-1,2,3-benzotriazin-3(4*H*)- il] etil} ácido pentanoico (Compuesto Nro.198), ----------

---

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(1-oxoftalazin-2(1*H*)-il)etil]ácido pentanoico (Compuesto Nro.199), ----------

-

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il)etil] ácido pentanoico (Compuesto Nro.200), ----------

---

(2*S*,3*R*)-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-il)etil]-3-hi-droxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro.201), ----------

-

(2*S*,3*R*)-2-[2-(2,4-dioxo-2*H*-1,3-benzoxazin-3(4*H*)-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro.202), ----------

-

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(3, 4,4-trimetil-2,5-dioxoimidazolidin-1-il)etil]ácido pentanoi-co (Compuesto Nro.203), ----------

---

(2S,3R)-2-[2-(5-fluoro-4-oxo-1,2,3-benzotriazin-3(4H)-il) e-til]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il]ácido

pen-tanoico (Compuesto Nro.211), ----------

(2S,3R)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro.212), ----------

---

(2S,3R)-3-hidroxi-5-(6'-metoxi-2,3'-bipiridin-5-il)-2-[2-(8-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoi-co (Compuesto Nro.213), ----------

---

(2*S*,3*R*)-3-hidroxi-5-[4-(6-hidroxipiridin-3-il)fenil]-2-[2-(4 -oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro.226), ----------

---

(2*S*,3*R*)-3-hidroxi-5-(4'-metilbifenil-4-il)-2-{2-[4- oxo- 7-(trifluorometil)-1,2,3-benzotriazin-3(4*H*)-il]etil}ácido pen-tanoico (Compuesto Nro.227), ----------

---

(2*S*,3*R*)-2-[2-(2,4-dioxo-1,4-dihidroquinazolin-3(2*H*)-il)etil] -3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido pentanoico (Compuesto Nro.228), ----------

---

(2*S*,3*R*)-3-(acetiloxi)-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2 -(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro.229), ----------

---

(2*S*,3*R*)-2-[2-(8-cloro-4-oxo-1,2,3-benzotriazin-3(4*H*)-il) e-til]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]ácido

penta-noico (Compuesto Nro.230),----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-2-[2-(2,4-dioxo-2*H*-1,3-ben-zoxazin-3(4*H*)-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro. 231), y ----------

---

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-(2-{[(2-hidroxi fenil)carbonil]amino}etil) ácido pentanoico (Compuesto Nro. 232). ----------

---

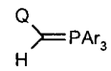
18. Un proceso para preparar un compuesto de la Fórmula XXVI que comprende: ----------

-

a) reaccionar un compuesto de la Fórmula XII con un compuesto de la Fórmula XXI ----------

-

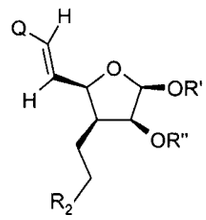
Con formato: Numeración y viñetas



Formula XXI

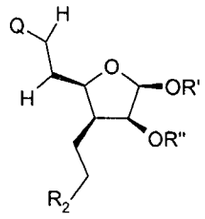
Para dar un compuesto de la Fórmula XXII; ----------

-



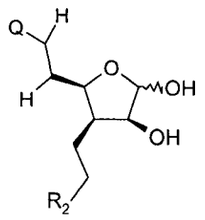
Formula XXII

b) hidrogenar el compuesto de la Fórmula XXII para dar un compuesto de la Fórmula XXIII; ----------



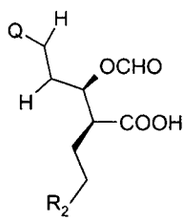
Formula XXIII

c) desproteger el compuesto de la Fórmula XXIII para dar un compuesto de la Fórmula XXIV; ----------



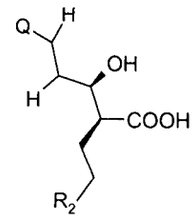
Formula XXIV

d) convertir el compuesto de la Fórmula XXIV en un compuesto de la Fórmula XXV; y ----------



Formula XXV

e) desformilar el compuesto de la Fórmula XXV para dar el compuesto de la Fórmula XXVI,.----------



Formula XXVI

en donde: ----------

-

R' y R" juntos forman un grupo protector acetal; ----------

-

R_2 es un heterociclilo o heteroarilo que contiene N; ------

--

Ar es fenilo; y ----------

-

Q es arilo o heteroarilo opcionalmente sustituido. --------

-

19. El proceso de acuerdo con la reivindicación 18, en donde los compuestos de la Fórmula XXVI se seleccionan de:

-

(2S,3R)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3 (4H) -il) etil]-5-fenil ácido pentanoico (Compuesto Nro. 82), ----------

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-fenil ácido pentanoico (Compuesto Nro.83), ----

(2*S*,3*R*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3 -hidroxi-5-[4(trifluorometil)fenil]ácido pentanoico (Com-

puesto Nro.84), ----------

-

(2*S*,3*R*)-5-(4-*tert*-butilfenil)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro.85), y ----------

(2S,3R)-5-(4-cloro-3-fluorofenil)-2-[2-(1,3-dioxo-1,3-dihi-dro-2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro.204). ----------

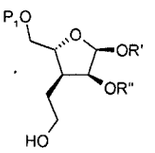
-

20. Un proceso para preparar un compuesto de la Fórmula XXXV que comprende: ----------

-

a. reaccionar un compuesto de la Fórmula VIIIb ---------

-



Formula VIIIb

Con un compuesto de la Fórmula IX ----------

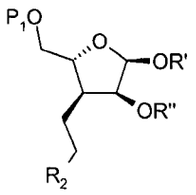
-

R_2-H

Formula IX

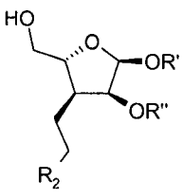
Para dar un compuesto de la Fórmula XXVII; ----------

-



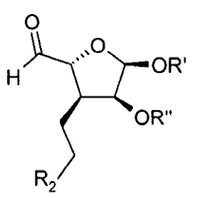
Formula XXVII

b. desproteger un compuesto de la Fórmula XXVII para dar un compuesto de la Fórmula XXVIII ----------



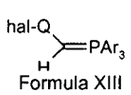
Formula XXVIII

c. oxidizar el compuesto de la Fórmula XXVIII para dar un compuesto de la Fórmula XXIX; ----------



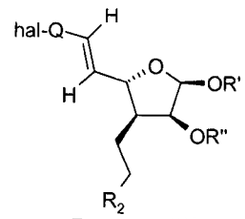
Formula XXIX

d. reaccionar el compuesto de la Fórmula XXIX con un compuesto de la Fórmula XIII ----------



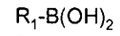
Formula XIII

Para dar un compuesto de la Fórmula XXX; ----------



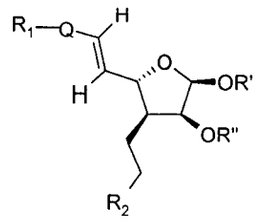
Formula XXX

e. reaccionar el compuesto de la Fórmula XXX con un compuesto de la Fórmula XV ----------



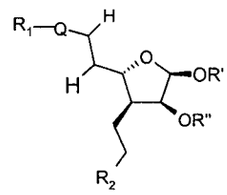
Formula XV

Para dar un compuesto de la Fórmula XXXI; ----------



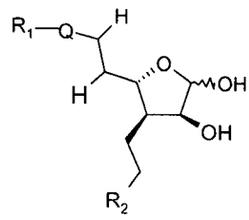
Formula XXXI

f. hidrogenar el compuesto de la Fórmula XXXI para dar un compuesto de la Fórmula XXXII; ----------



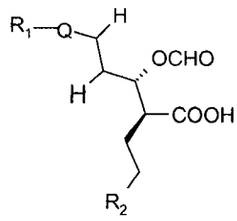
Formula XXXII

g. desproteger el compuesto de la Fórmula XXXII para dar un compuesto de la Fórmula XXXIII; ----------



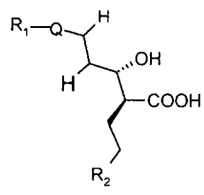
Formula XXXIII

h. convertir el compuesto de la Fórmula XXXIII para dar un compuesto de la Fórmula XXXIV; y ----------



Formula XXXIV

i. desformilar el compuesto de la Fórmula XXXIV para dar un compuesto de la Fórmula XXXV, ----------



Formula XXXV

En donde ----------

P_1 es un grupo protector sililo; ----------

R' y R" juntos forman un grupo protector acetal; ----------

-

R_2 es heterociclilo o heteroarilo que contiene N; ---------

--

hal es Cl, Br o I; ----------

-

Ar es fenilo; ----------

-

Q es arilo o heteroarilo opcionalmente sustituido; y ------

-

R_1 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heterociclilo, heteroarilo, aralquilo, alcoxi, ariloxi, alqueniloxi o alquiniloxi opcionalmente sustituido.

21. El proceso de acuerdo con la reivindicación 20, en donde los compuestos de la Fórmula XXXV se seleccionan de:

-

(2*S*,3*S*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro.143), ----------

---

(2*S*,3*S*)-3-hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(4-oxo-1,2, 3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Compuesto Nro. 208). ----------

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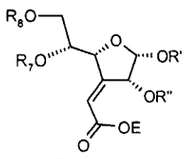
22. Un proceso para preparar un compuesto de la Fórmula LIII que comprende: ----------

-

a) convertir un compuesto de la Fórmula XLI en un compuesto de la Fórmula XLII ----------

Con formato: Numeración y viñetas

-



Formula XLII

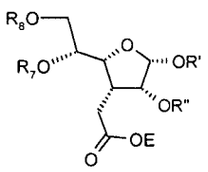
mediante reacción con un agente de *Wittig*; ----------

-

b) hidrogenar el compuesto de la Fórmula XLII para dar un compuesto de la Fórmula XLIII; ----------

Con formato: Numeración y viñetas

-

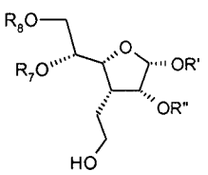


Formula XLIII

c) reducir el compuesto de la Fórmula XLIII para dar un compuesto de la Fórmula XLIV; ----------

Con formato: Numeración y viñetas

-



Formula XLIV

d) reaccionar el compuesto de la Fórmula XLIV con un compuesto de la Fórmula IX ----------

Con formato: Numeración y viñetas

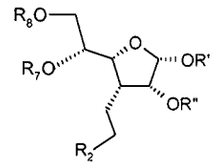
-

R_2-H

Formula IX

Para dar un compuesto de la Fórmula XLV; ----------

-

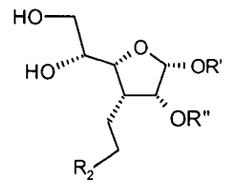


Formula XLV

e) desproteger el compuesto de la Fórmula XLV para dar un compuesto de la Fórmula XLVI; ----------

Con formato: Numeración y viñetas

-

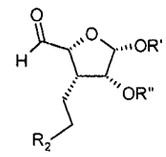


Formula XLVI

f) oxidizar el compuesto de la Fórmula XLVI para dar un compuesto de la Fórmula XLVII; ----------

Con formato: Numeración y viñetas

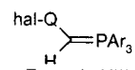
-



Formula XLVII

g) reaccionar el compuesto de la Fórmula XLVII con un compuesto de la Fórmula XIII ----------

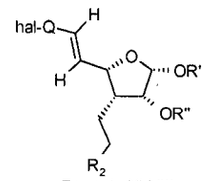
-



Formula XIII

Para dar un compuesto de la Fórmula XLVIII; ----------

-



Formula XLVIII

h) reaccionar el compuesto de la Fórmula XLVIII con un compuesto de la Fórmula XV ----------

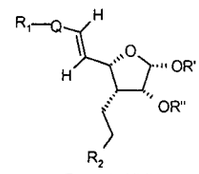
-

R_1-B(OH)$_2$

Formula XV

Para dar un compuesto de la Fórmula XLIX; ----------

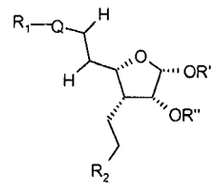
-



Formula XLIX

i) hidrogenar el compuesto de la Fórmula XLIX para dar un compuesto de la Fórmula L; ----------

-

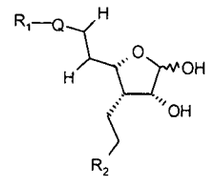


Formula L

j) desproteger el compuesto de la Fórmula L para dar un compuesto de la Fórmula LI; ----------

Con formato: Numeración y viñetas

-

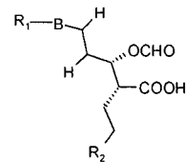


Formula LI

k) convertir el compuesto de la Fórmula LI en un compuesto de la Fórmula LII; y ----------

Con formato: Numeración y viñetas

-

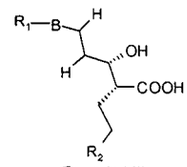


Formula LII

l) desformilar el compuesto de la Fórmula LII para dar el compuesto de la Fórmula LIII, ----------

Con formato: Numeración y viñetas

-



Formula LIII

en donde: ----------

-

R_7 y R_8 juntos forman un grupo protector acetal; ----------

--

R' y R" juntos foman un grupo protector acetal; ----------

-

E es un grupo alquilo; ----------

-

R_2 es un heterociclilo o heteroarilo que contiene N; ------

-

hal es Cl, Br o I; ----------

-

Ar es fenilo; ----------

-

Q es arilo o heteroarilo opcionalmente sustituido; y ------

-

R_1 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heterociclilo, heteroarilo, aralquilo, alcoxi, ariloxi, alqueniloxi o alquiniloxi opcionalmene sustituido.

23. El proceso de acuerdo con la reivindicación 22, en donde los compuestos de la Fórmula LIII se seleccionan de:

-

(2*R*,3*S*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro. 120), ----------

---

(2R,3S)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5 -(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi ácido

pentanoico (Compuesto Nro.205), ----------

(2*R*,3*S*)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxi ácido pentanoico (Compuesto Nro.206), y ----------

-

(2*R*,3*S*)-5-(3',4'-difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro.207). ----------

-

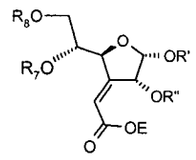
24. Un proceso para preparar un compuesto de la Fórmula LXVI que comprende: ----------

-

a) convertir un compuesto de la Fórmula XXXVII en un compuesto de la Fórmula LIV ----------

-

Con formato: Numeración y viñetas



Formula LIV

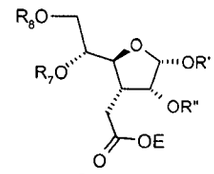
Mediante reacción con un reactivo de *Wittig*; ----------

-

b) hidrogenar el compuesto de la Fórmula LIV para dar un compuesto de la Fórmula LV; ----------

-

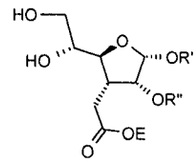
Con formato: Numeración y viñetas



Formula LV

c) desproteger el compuesto de la Fórmula LV para dar un compuesto de la Fórmula LVI; ----------

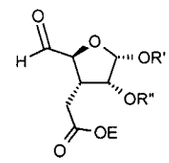
-



Formula LVI

d) oxidizar el compuesto de la Fórmula LVI para dar un compuesto de la Fórmula LVII; ----------

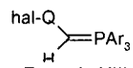
-



Formula LVII

e) reaccionar el compuesto de la Fórmula LVII con un compuesto de la Fórmula XIII ----------

-

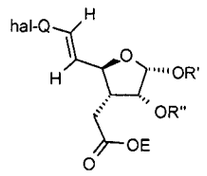


Formula XIII

Para dar un compuesto de la Fórmula LVIII; ----------

-

572

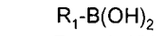


Formula LVIII

f) reaccionar el compuesto de la Fórmula LVIII con un compuesto de la Fórmula XV ----------

Con formato: Numeración y viñetas

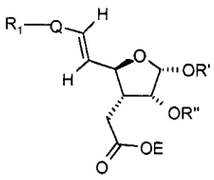
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Formula XV

Para dar un compuesto de la Fórmula LIX; ----------

-

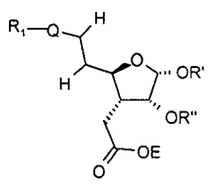


Formula LIX

g) hidrogenar el compuesto de la Fórmula LIX para dar un compuesto de la Fórmula LX; ----------

Con formato: Numeración y viñetas

-

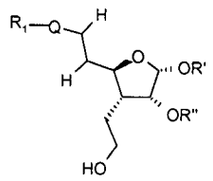


Formula LX

h) desproteger el compuesto de la Fórmula LX para dar un compuesto de la Fórmula LXI; ----------

Con formato: Numeración y viñetas

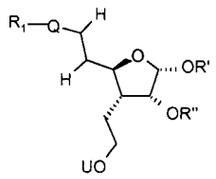
-



Formula LXI

i) activar el compuesto de la Fórmula LXI en un compuesto de la Fórmula LXII; ----------

Con formato: Numeración y viñetas



Formula LXII

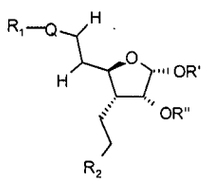
j) reaccionar el compuesto de la Fórmula LXII con un compuesto de la Fórmula IXa. ----------

Con formato: Numeración y viñetas

R_2-M

Formula IXa

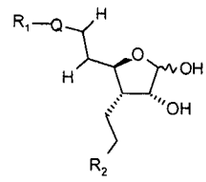
Para dar un compuesto de la Fórmula LXIII; ----------



Formula LXIII

k) desproteger el compuesto de la Fórmula LXIII para dar un compuesto de la Fórmula LXIV; ----------

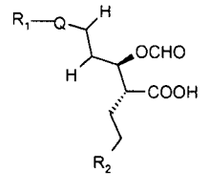
Con formato: Numeración y viñetas



Formula LXIV

l) convertir el compuesto de la Fórmula LXIV en un compuesto de la Fórmula LXV; y ----------

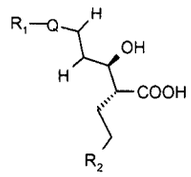
Con formato: Numeración y viñetas



Formula LXV

m) desformilar el compuesto de la Fórmula LXV para dar un compuesto de la Fórmula LXVI, ----------

Con formato: Numeración y viñetas



Formula LXVI

en donde ----------

R_7 y R_8 juntos forman un grupo protector acetal; ----------

R' y R" juntos forman un grupo protector acetal; ----------

R_2 es un heterociclilo o heteroarilo que contiene N; ------

U es un grupo activador de O; ----------

-

E es un grupo alquilo; ----------

-

hal es Cl, Br o I; ----------

-

Ar es fenilo; ----------

-

M es un metal; ----------

-

Q es arilo o heteroarilo opcionalmente sustituido; y ------

-

R_1 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heterociclilo, heteroarilo, aralquilo, alcoxi, ariloxi, alqueniloxi o alquiniloxi opcionalmente sustituido.

25. El proceso de acuerdo con la reivindicación 24, en donde los compuestos de la Fórmula LXVI se seleccionan de:

-

(2R,3R)-5-(4'-clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro -2H-isoindol-2-il)etil]-3-hidroxi ácido pentanoico (Compuesto Nro.89), y ----------

-

(2*R*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro.96). ----------

---

26. Un proceso para preparar un compuesto de la Fórmula XX que comprende: ----------

-

a) reaccionar un compuesto de la Fórmula LXVII ----------

Con formato: Numeración y viñetas

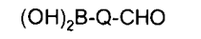
-



Formula LXVII

Con un compuesto de la Fórmula LXVIII ----------

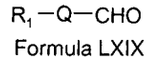
-



Formula LXVIII

Para dar un compuesto de la Fórmula LXIX; ----------

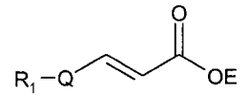
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Formula LXIX

b) convertir el compuesto de la Fórmula LXIX en un compuesto de la Fórmula LXX; ----------

Con formato: Numeración y viñetas

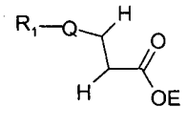


Formula LXX

c) hidrogenar el compuesto de la Fórmula LXX para dar un compuesto de la Fórmula LXXI; ----------

Con formato: Numeración y viñetas

-

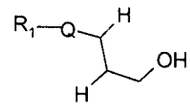


Formula LXXI

d) reducir el compuesto de la Fórmula LXXI para dar un compuesto de la Fórmula LXXII; ----------

Con formato: Numeración y viñetas

-

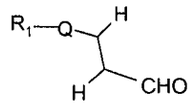


Formula LXXII

e) oxidizar el compuesto de la Fórmula LXXII para dar un compuesto de la Fórmula LXXIII; ----------

Con formato: Numeración y viñetas

-

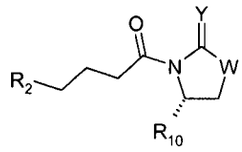


Formula LXXIII

f) reaccionar el compuesto de la Fórmula LXXIII con un compuesto de la Fórmula LXXIV ----------

Con formato: Numeración y viñetas

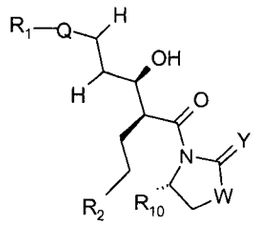
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Formula LXXIV

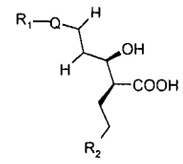
Para dar un compuesto de la Fórmula LXXV; y ----------

-



Formula LXXV

g) hidrolizar el compuesto de la Fórmula LXXV para dar un compuesto de la Fórmula XX, ----------



Formula XX

en donde: ----------

R_2 es un heterociclilo o heteroarilo que contiene N, ----------

E es un grupo alquilo; ----------

hal es Cl, Br o I; ----------

Q es un arilo o heteroarilo opcionalmente sustituido; ----------

R_1 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heterociclilo, heteroarilo, aralquilo, alcoxi, ariloxi, alqueniloxi, alqueniloxi o alquiniloxi opcionalmente sustituido; ----------

Y y W son independientemente oxígeno o azufre; y ----------

R_{10} es alquilo, arilo o aralquilo. ----------

27. El proceso de acuerdo con la reivindicación 26 en donde los compuestos de la Fórmula XX se seleccionan de: ----------

(2S,3R)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]ácido pentanoico (Com-puesto Nro.86), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(5-metilpiridin-2-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro.209), ----------

(2*S*,3*R*)-5-[4-(6-fluoropiridin-3-il)fenil]-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]ácido pentanoico (Com-puesto Nro.210), ----------

(2*S*,3*R*)-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Com-puesto Nro.214), ----------

(2*S*,3*R*)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il) me-til]-5-[4'-(trifluorometil)bifenil-4-il]ácido pentanoico (Compuesto Nro.215),----------

(2*S*,3*R*)-5-(2',4'-difluorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compues-to Nro.216),----------

((2*S*,3*R*)-5-(4'-fluorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3 -benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compuesto Nro. 217), ----------

(2*S*,3*R*)-5-(3'-fluoro-64'-metoxibifenil-4-il)-3-hidroxi-2-[(4 -oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compuesto Nro.218), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(2-metoxipirimidin-5-il)fenil]-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compuesto Nro.219), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2- [(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Com-puesto Nro.220), ----------

(2*S*,3*R*)-3-hidroxi-5-(4'-metilbifenil-4-il)-2- [(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compuesto Nro. 221), ----------

(2*S*,3*R*)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il) me-til]-5-[4'-(trifluorometoxi)bifenil-4-il]ácido pentanoico (Compuesto Nro.222), ----------

(2*S*,3*R*)-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]-2-[(4-oxo -1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Com-puesto Nro.223),----------

(2*S*,3*R*)-5-(4'-clorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compuesto Nro. 224), y ----------

(2*S*,3*R*)-5-(3',4'-difluorobifenil-4-il)-3-hidroxi-2-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)metil]ácido pentanoico (Compues-to Nro. 225). ----------

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Extracto. ----------

El presente invento se relaciona con ácidos carboxílicos sustituidos mediante β-hidroxi y amino, que actúan como inhibidores de la metaloproteasa matriz, ácidos carboxílicos β-hidroxi diastereoméricamente puros, procesos correspondientes para la síntesis de composiciones farmacéuticas que contienen los compuestos del presente invento. Los compuestos del presente invento son útiles en el tratamiento de diversas enfermedades inflamatorias, de autoinmunidad y alérgicas, como ser los métodos para tratar el asma, la artritis reumatoidea, COPD, rinitis, osteoartritis, artritis soriásica, psoriasis, fibrosis pulmonar, desórdenes en la cura de heridas, inflamación pulmonar, síndrome de perturbación respiratoria agudo, periodontitis, esclerosis múltiple, gingivitis,

ateroesclerosis, proliferación neoíntima, que lleva a la restenosis y a la insuficiencia cardíaca isquémica, ataque apopléjico, enfermedades renales, metástasis tumoral y otros desórdenes inflamatorios caracterizados por la hiper-expresión e hiper-activación de una metaloproteinasa matriz utilizando los compuestos. ----------

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Es traducción fiel del Inglés al Castellano del documento adjunto, redactado en idioma Inglés, que he tenido a la vista y al cual me remito. En la ciudad de Buenos Aires, a los cuatro días del mes de setiembre de dos mil siete. ----

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
RLL-895WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2007/053340	21/08/2007	22/08/2006
Applicant		
RANBAXY LABORATORIES LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/053340

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/48 C07D401/06 A61K31/4035 A61P29/00

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/026120 A (GLAXO GROUP LTD [GB]; GAINES SIMON [GB]; HOLMES IAN PETER [GB]; MARTIN) 24 March 2005 (2005-03-24) page 1, lines 5-8; claims 1-10; examples 1-12	1,9-13
P,X	WO 2006/090235 A (RANBAXY LAB LTD [IN]; PALLE VENKATA P [IN]; SATTIGERI VISWAJANANI JITE) 31 August 2006 (2006-08-31) page 4, lines 18-27; claims 1-11; examples 1-8	1,6,9-13

☐ 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 January 2008	05/02/2008

Name and mailing address of the ISA	Authorized officer
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	Cooper, Simon

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2007/053340

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005026120 A	24-03-2005	AU 2004272280 A1	24-03-2005
		BR PI0413791 A	07-11-2006
		CA 2538315 A1	24-03-2005
		CN 1849306 A	18-10-2006
		EP 1663970 A1	07-06-2006
		IS 8268 A	26-01-2006
		JP 2007505081 T	08-03-2007
		KR 20060120648 A	27-11-2006
		MX PA06002458 A	20-06-2006
		US 2006293353 A1	28-12-2006
WO 2006090235 A	31-08-2006	CA 2598518 A1	31-08-2006
		EP 1856063 A1	21-11-2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-017757- -00000-0000

Fecha: 2009-02-23 15:48:20 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 586

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Claudia M Neva Cortes
Firma Responsable

Fecha_____

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CARDENAS NAVAS DARIO
Apoderado(a) y/o Representante de
RANBAXY LABORATORIES LIMITED

REFERENCIA	Radicación No.	9 17757
	Solicitud internacional	PCT/IB2007/053340
	Fecha inicio fase nacional	22/03/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	3802

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 27 MAR. 2009
adpa11