SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-165101- -00000-0000
Fecha: 2011-11-30 16:58:17 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 364
Act. 411 PRESENTACION Folios: 405

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DIVISIONAL DE PATENTE DE INVENCIÓN

TITULO: **DERIVADOS AMINO-PROPIÓNICOS SUSTITUIDOS COMO INHIBIDORES DE NEPRILISINA.**

SOLICITANTE: NOVARTIS AG

DIRECCIÓN: Lichtstrasse 35, CH- 4056 Basel, Suiza

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 30 de noviembre de 2011

P2011/000208

OLARTEMO
OLARTE MOURE & ASOCIAD

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-165101- -00000-0000
Fecha: 2011-11-30 16:58:17 Dep. 2020 DIR.NUEVASCR
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Act. 411 PRESENTACION Folios: 405

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000208**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: NOVARTIS AG
Dirección: Lichtstrasse 35, CH-4056 Basel
Nacionalidad o Domicilio: Suiza
Lugar de Constitución: Suiza
Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

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C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA.
Dirección: VER PAGINA ADJUNTA.
Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2010/057247 Fecha Mayo 26, 2010

Publicación Internacional No. WO 2010/136493 Fecha Diciembre 02, 2010

(6) **Título (54) DERIVADOS AMINO-PROPIÓNICOS SUSTITUIDOS COMO INHIBIDORES DE NEPRILISINA.**

Clasificación Internacional (51) C07D 213/82, C07D 239/36, C07D 261/18, C07D 271/06, C07C 233/47, A61K 31/21, A61K 31/435.

Prioridad
SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Mayo 28, 2009	61/181,756
US	Noviembre 20, 2009	61/263,145
US	Abril 16, 2010	61/324,943

(9) **Comprobante de pago No.** 11- **Fecha** Noviembre de 2011

(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. VER EXP. Nº08-102.832
- [x] Documento de cesión del inventor al solicitante o a su causante. DECLARACION REGLA 4.17
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] 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.
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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PCT/EP2010/057247

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Nacionalidad: Estadounidense

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 115952

Bogotá D.C., Noviembre 29 de 2011 - 14:40:25

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	408396074	29/11/2011	4.599.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr UNDITARIO	Vr CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	571.000.00	571.000.00
				$571.000.00

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: _____
- *** -

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-165101- -00000-0000
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Act. 411 PRESENTACION Eve: 378 FASENACIONALI
Folios: 364
Act. 411 PRESENTACION Folios: 405

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

Nota del traductor:

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusticia

4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

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E-mail: treseser1@yahoo.com. No. 8346

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahin
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahin
Graciela Melo

Power of Attorney

Poder

The undersigned,

El suscrito,

NOVARTIS AG

domiciled in

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Arthur Canonica

Pascal Traub

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Attestation

1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.

2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.

3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)

M. Staehelin Notar

Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven), 2009 (two thousand and nine).

Leg.Prot.Nr. 975 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by .....
3. in his/her function as .....
4. and certified by the seal of the .....

Certified 3 0. Nov. 2005

5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. P 0491 18'389
9. Seal / stamp: 10. Signature:

Heidi Fischer

STATE CHANCERY * BASLE-CITY *

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application NOVARTIS AG is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from COPPOLA, Gary Mark to NOVARTIS AG, dated 21 April 2010 (21.04.2010)
VIII-2-1(iv)		an assignment from IWAKI, Yuki to NOVARTIS AG, dated 23 April 2010 (23.04.2010)
VIII-2-1(iv)		an assignment from KARKI, Rajeshri Ganesh to NOVARTIS AG, dated 23 April 2010 (23.04.2010)
VIII-2-1(iv)		an assignment from KAWANAMI, Toshio to NOVARTIS AG, dated 23 April 2010 (23.04.2010)
VIII-2-1(iv)		an assignment from KSANDER, Gary Michael to NOVARTIS AG, dated 23 April 2010 (23.04.2010)
VIII-2-1(iv)		an assignment from MOGI, Muneto to NOVARTIS AG, dated 23 April 2010 (23.04.2010)
VIII-2-1(iv)		an assignment from SUN, Robert to NOVARTIS AG, dated 23 April 2010 (23.04.2010)

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 December 2010 (02.12.2010)

PCT

(10) International Publication Number
WO 2010/136493 A1

(51) International Patent Classification:
C07D 213/82 (2006.01) *C07C 233/47* (2006.01)
C07D 239/36 (2006.01) *A61K 31/21* (2006.01)
C07D 261/18 (2006.01) *A61K 31/435* (2006.01)
C07D 271/06 (2006.01)

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(22) International Filing Date:
26 May 2010 (26.05.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/181,756	28 May 2009 (28.05.2009)	US
61/263,145	20 November 2009 (20.11.2009)	US
61/324,943	16 April 2010 (16.04.2010)	US

(71) Applicants *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH). **SUN, Robert** [US/US]; Novartis Institutes for BioMedical Research, Inc., 100 Technology Square, Cambridge, Massachusetts 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **COPPOLA, Gary Mark** [US/US]; 18 Aldersgate Circle, Budd Lake, New Jersey 07828 (US). **IWAKI, Yuki** [JP/US]; Novartis Institutes for BioMedical Research, Inc., 400 Technology Square, Cambridge, Massachusetts 02139 (US). **KARKI, Rajeshri Ganesh** [IN/US]; Novartis Institutes for BioMedical Research, Inc., 100 Technology Square, Cambridge, Massachusetts 02139 (US). **KAWANAMI, Toshio** [JP/US]; Novartis Institutes for BioMedical Research, Inc., 100 Technology Square, Cambridge, Massachusetts 02139 (US). **KSANDER, Gary Michael** [US/US]; Novartis Institutes for BioMedical Research, Inc., 100 Technology Square, Cambridge, Massachusetts 02139 (US). **MOGI, Muneto** [JP/US]; Novartis Institutes for BioMedical Research, Inc., 100 Technology Square, Cambridge, Massachusetts 02139 (US).

(74) Agent: **VOEGELI-LANGE, Regina**; Novartis Pharma AG, Patent Department, CH-4002 Basel (CH).

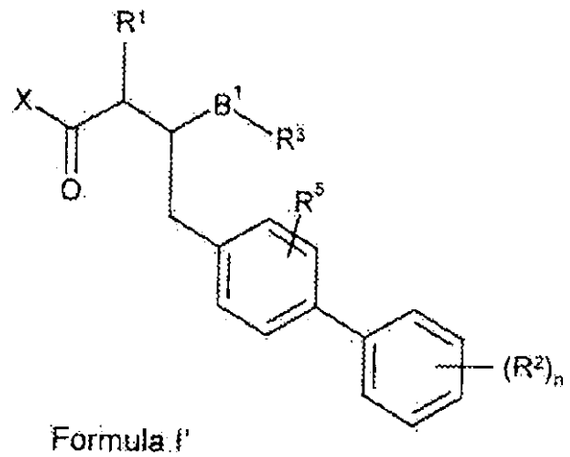
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

[Continued on next page]

(54) Title: SUBSTITUTED AMINOPROPIONIC DERIVATIVES AS NEPRILYSIN INHIBITORS



Formula I'

(57) Abstract: The present invention provides a compound of formula I' or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^5, B^1, X and n are defined herein. The invention also relates a method for manufacturing the compounds of the invention, and its therapeutic uses. The present invention further provides a combination of pharmacologically active agents and a pharmaceutical composition.

WO 2010/136493 A1

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

SUBSTITUTED AMINOPROPIONIC DERIVATIVES AS NEPRILYSIN INHIBITORS

BACKGROUND OF THE INVENTION

Endogenous atrial natriuretic peptides (ANP), also called atrial natriuretic factors (ANF) have diuretic, natriuretic and vasorelaxant functions in mammals. The natural ANF peptides is metabolically inactivated, in particular by a degrading enzyme which has been recognized to correspond to the enzyme neutral endopeptidase (NEP) EC 3.4.24.11, also responsible for *e.g.* the metabolic inactivation of enkephalins.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopeptidase; NEP) is a zinc-containing metalloprotease that cleaves a variety of peptide substrates on the amino side of hydrophobic residues [see *Pharmacol Rev*, Vol. 45, p. 87 (1993)]. Substrates for this enzyme include, but are not limited to, atrial natriuretic peptide (ANP, also known as ANF), brain natriuretic peptide (BNP), met- and leu-enkephalin, bradykinin, neurokinin A, endothelin-1 and substance P. ANP is a potent vasorelaxant and natriuretic agent [see *J Hypertens*, Vol. 19, p. 1923 (2001)]. Infusion of ANP in normal subjects resulted in a reproducible, marked enhancement of natriuresis and diuresis, including increases in fractional excretion of sodium, urinary flow rate and glomerular filtration rate [see *J Clin Pharmacol*, Vol. 27, p. 927 (1987)]. However, ANP has a short half-life in circulation, and NEP in kidney cortex membranes has been shown to be the major enzyme responsible for degrading this peptide [see *Peptides*, Vol. 9, p. 173 (1988)]. Thus, inhibitors of NEP (neutral endopeptidase inhibitors, NEPi) should increase plasma levels of ANP and, hence, are expected to induce natriuretic and diuretic effects.

This enzyme is involved in the breakdown of several bioactive oligopeptides, cleaving peptide bonds on the amino side of hydrophobic amino acid residues. The peptides metabolised include atrial natriuretic peptides (ANP), bombesin, bradykinin, calcitonin gene-related peptide, endothelins, enkephalins, neurotensin, substance P and vasoactive intestinal peptide. Some of these peptides have potent vasodilatory and neurohormone functions, diuretic and natriuretic activity or mediate behaviour effects.

SUMMARY OF THE INVENTION:

The aim of the present invention is to provide novel compounds which are useful as neutral endopeptidase inhibitors, e.g. as inhibitors of the ANF-degrading enzyme in mammals, so as to prolong and potentiate the diuretic, natriuretic and vasodilator properties of ANF in mammals, by inhibiting the degradation thereof to less active metabolites.

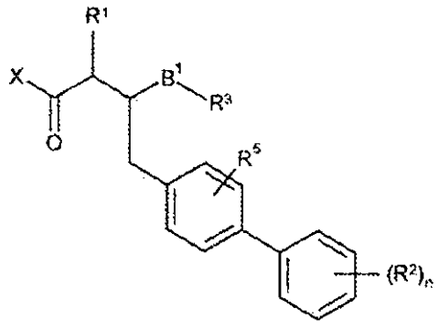
The compounds of this invention are thus particularly useful for the treatment of conditions and disorders responsive to the inhibition of neutral endopeptidase (NEP) EC 3.4.24.11.

Thus, the compounds of the invention, by inhibiting the neutral endopeptidase EC.3.4.24.11, can potentiate the biological effects of bioactive peptides. Thus, in particular the compounds have utility in the treatment of a number of disorders, including hypertension, pulmonary hypertension, isolated systolic hypertension, resistant hypertension, peripheral vascular disease, heart failure, congestive heart failure, left ventricular hypertrophy, angina, renal insufficiency (diabetic or non-diabetic), renal failure (including edema and salt retension), diabetic nephropathy, non-diabetic nephropathy, nephroic syndrome, glomerulonephritis, scleroderma, glomerular sclerosis, proteinurea of primary renal disease, renal vascular hypertention, diabetic retinopathy and end-stage renal disease (ESRD), endothelial dysfunction, diastolic dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation (AF), cardiac fibrosis,atrial flutter, detrimental vascular remodeling, plaque stabilization, myocardial infarction (MI), renal fibrosis, polycystic kidney disease (PKD), pulmonary arterial hypertension, renal failure (including edema and salt retension), cyclical oedema, Menières disease, hyperaldosteroneism (primary and secondary) and hypercalciuria, ascites. In addition, because of their ability to potentiate the effects of ANF the compounds have utility in the treatment of glaucoma. As a further result of their ability to inhibit the neutral endopeptidase E.C.3.4.24.11 the compounds of the invention may have activity in other therapeutic areas including for example the treatment of menstrual disorders, preterm labour, pre-eclampsia, endometriosis, and reproductive disorders (especially male and female infertility, polycystic ovarian syndrome, implantation failure). Also the compounds of the invention should treat asthma, obstructive sleep apnea, inflammation, leukemia, pain, epilepsy, affective disorders such as depression and psychotic condition such as dementia and geriatric confusion, obesity and gastrointestinal disorders (especially diarrhea and irritable bowel syndrome), wound healing (especially diabetic and venous ulcers and pressure sores), septic shock, the modulation of gastric acid secretion, the treatment of hyperreninaemia, cystic fibrosis, restenosis, type-2 diabetes, metabolic syndrome, diabetic complications and athereosclerosis, male and female sexual dysfunction. In a preferred embodiment the compounds of the invention are useful in the treatment of cardiovascular disorders.

The invention pertains to the compounds, methods for using them, and uses thereof as described herein. Examples of compounds of the invention include the compounds

accoring to anyone of Formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, and the compounds of the examples.

The invention therefore provides a compound of the formula (I'):



Formula I'

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, -SH, -S-C_{1-7}alkyl or NR^aR^b;
R^2 for each occurence, is independently C_{1-7}alkyl, halo, NO_2, CN, C_{1-7}alkanoylamino, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, -NR^aR^b, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^a and R^b for each occurrence are independently H or C_{1-7}alkyl;
R^3 is A^1-C(O)X^1 or A^2-R^4;
R^4 is C_{6-10}aryl or a heteroaryl, which can be monocyclic or bicyclic, and which can be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, hydroxyC_{1-7}alkyl, nitro, -NR^aR^b, -C(O)C_{1-7}alkyl, C(O)-O-C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{2-7}alkenyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl; or R^4 is a heterocyclyl which can be optionally substituted with one or more substituents independently selected from the group consisting of oxo, hydroxy, hydroxyC_{1-7}alkyl, amino, C(O)-O- C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl;
R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and
X and X^1 are independently OH, -O-C_{1-7}alkyl, -NR^aR^b, -$NHS(O)_2$-C_{1-7}alkyl, -$NHS(O)_2$-benzyl or -O- C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_{6-10}aryl, heteroaryl, heterocyclyl, $C(O)NH_2$, C(O)NH- C_{1-6}alkyl, and C(O)N(C_{1-6}alkyl)$_2$;
B^1 is –C(O)NH- or –NHC(O)-;

A^1 is a bond or a linear or branched C_{1-7}alkylene ; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{3-7}cycloalkyl, C_{1-7}alkoxy, hydroxy and O-acetate; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

A^1 is a linear or branched C_{1-7}alkenylene; or

A^1 is a linear C_{1-4} alkylene wherein one or more carbon atom(s) is/are replaced with an heteroatom selected from O, NR^c; and A^1 is optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{1-7}alkyl; in which R^c for each occurrence, is independently H, C_{1-7}alkyl, -C(O)-O-C_{1-7}alkyl or -$CH_2C(O)OH$; or

A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, $-NR^aR^b$, $-OCH_2CO_2H$, and $-OCH_2C(O)NH_2$; or

A^1 is a C_{3-7}cycloalkyl;

A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein A^1 may be in either direction; and

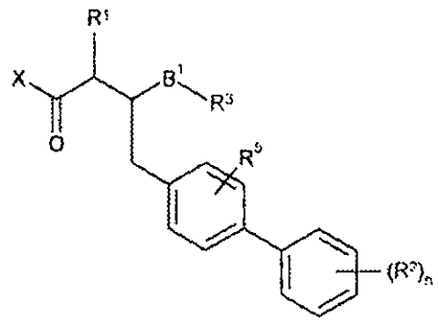
A^2 is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

n is 0, 1, 2, 3, 4 or 5;

wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

The invention therefore provides a compound of the formula (I):



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or C_{1-7}alkyl;

R^2 for each occurence, is independently C_{1-7}alkyl, halo, NO_2, CN, C_{1-7}alkanoylamino, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, $-NR^aR^b$, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^a and R^b for each occurrence are independently H or C_{1-7}alkyl;

R^3 is A^1-C(O)X^1 or A^2-R^4;

R^4 is C_{6-10}aryl or a heteroaryl, which can be monocyclic or bicyclic, and which can be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, hydroxyC_{1-7}alkyl, amino, C(O)-O- C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, $-NHSO_2$-C_{1-7}alkyl and benzyl; or R^4 is a heterocyclyl which can be optionally substituted with one or more substituents independently selected from the group consisting of oxo, hydroxy, hydroxyC_{1-7}alkyl, amino, C(O)-O- C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, $-NHSO_2$-C_{1-7}alkyl and benzyl;

R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and

X and X^1 are independently OH, -O-C_{1-7}alkyl, NR^aR^b, or -O- C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_{6-10}aryl, heteroaryl, heterocyclyl, $C(O)NH_2$, C(O)NH- C_{1-6}alkyl, and C(O)N(C_{1-6}alkyl)$_2$;

B^1 is –C(O)NH- or –NHC(O)-;

A^1 is a bond or a linear or branched C_{1-7}alkylene ; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{3-7}cycloalkyl, C_{1-7}alkoxy, hydroxy and O-acetate; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, $-NR^aR^b$, $-OCH_2CO_2H$, and $-OCH_2C(O)NH_2$; or

A^1 is a C_{3-7}cycloalkyl;

A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein A^1 may be in either direction; and

A^2 is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

n is 0, 1, 2, 3, 4 or 5;

wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

In another embodiment, the invention pertains to a method for treating a disorders or diseases responsive to the inhibition of neutral endopeptidase EC 3.4. 24.11 (NEP), in a subject, by administering to the subject a therapeutically effective amount of a compound according to anyone of Formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, such that the disorder or disease responsive to the inhibition of neutral endopeptidase EC 3.4. 24.11 (NEP) in the subject is treated.

In yet another embodiment, the invention pertains to a method for treating hypertension, pulmonary hypertension, isolated systolic hypertension, resistant hypertension, peripheral vascular disease, heart failure, congestive heart failure, left ventricular hypertrophy, angina, renal insufficiency (diabetic or non-diabetic), renal failure (including edema and salt retension), diabetic nephropathy, non-diabetic nephropathey, nephroic syndrome, glomerulonephritis, scleroderma, glomerular sclerosis, proteinurea of primary renal disease, renal vascular hypertention, diabetic retinopathy and end-stage renal disease (ESRD), endothelial dysfunction, diastolic dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation (AF), cardiac fibrosis,atrial flutter, detrimental vascular remodeling, plaque stabilization, myocardial infarction (MI), renal fibrosis, polycystic kidney disease (PKD), pulmonary arterial hypertension, renal failure (including edema and salt retension), cyclical oedema, Menières disease, hyperaldosteroneism (primary and secondary) and hypercalciuria, ascites, glaucoma, menstrual disorders, preterm labour, pre-eclampsia, endometriosis, and reproductive disorders (especially male and female infertility, polycystic ovarian syndrome, implantation failure), asthma, obstructive sleep apnea, inflammation, leukemia, pain, epilepsy, affective disorders such as depression and psychotic condition such as dementia and geriatric confusion, obesity and gastrointestinal disorders (especially diarrhea and irritable bowel syndrome), wound healing (especially diabetic and venous ulcers and pressure sores), septic shock, gastric acid secretion dysfunction, hyperreninaemia, cystic fibrosis, restenosis, type-2 diabetes, metabolic syndrome, diabetic complications and

atherosclerosis, male and female sexual dysfunction; comprising administering to the subject a therapeutically effective amount of a compound according to anyone of of Formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, such that the subject is treated.

In yet another embodiment, the invention pertains to pharmaceutical compositions, comprising of a compound according to anyone of Formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

In still another embodiment, the invention pertains to combinations including a compound according to anyone of Formulae I' and I-VIC, or a pharmaceutically acceptable salt thereof, and pharmaceutical combinations of one or more therapeutically active agents.

In another embodiment, the invention pertains to a method for inhibiting neutral endopeptidase EC 3.4. 24.11 in a subject by administering to the subject a therapeutically effective amount of a compound according to anyone of Formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, such that neutral endopeptidase EC 3.4. 24.11 is inhibited.

DETAILED DESCRIPTION OF THE INVENTION:

Compounds of the Invention

References hereinafter to compounds of Formula I or I' apply equally to compounds according to anyone of Formulae IA to VIIC.

References hereinafter to embodiments of the invention apply equally to compounds of Formula I or I' and compounds according to anyone of Formulae IA to VIIC, insofar as the embodiments are present.

Various embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments.

In one embodiment the invention provides a compound of the Formula I or I', or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{R^1}$ is H or C_{1-7}alkyl;

$\mathbf{R^2}$ for each occurence, is independently C_{1-7}alkyl, halo, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, -NR^aR^b, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^a and R^b for each occurence are independently H or C_{1-7}alkyl;

$\mathbf{R^3}$ is A^1-$C(O)X^1$ or A^2-R^4;

R^4 is C_{6-10}aryl or a heteroaryl, which can be monocyclic or bicyclic and which can be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl;

R^5 is H; and

X and X^1 are independently OH, -O-C_{1-7}alkyl or NR^aR^b;

B^1 is –C(O)NH- or –NHC(O)-;

A^1 is a linear or branched C_{1-7}alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{3-7}cycloalkyl, C_{1-7}alkoxy, hydroxy and O-acetate; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, $-NR^aR^b$, $-OCH_2CO_2H$, and $-OCH_2C(O)NH_2$; and

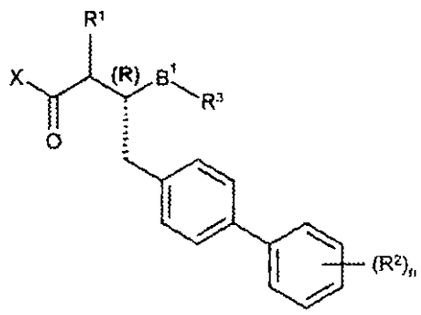
A^2 is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl; and

n is 0, 1, 2, 3, 4 or 5;

wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

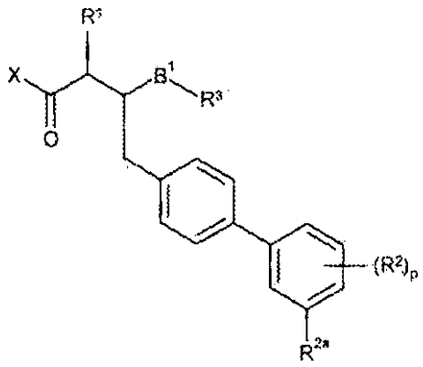
Certain compounds of Formula I or I' include compounds of Formula IA wherein the stereochemistry at the carbon bearing the biphenyl group is (R):



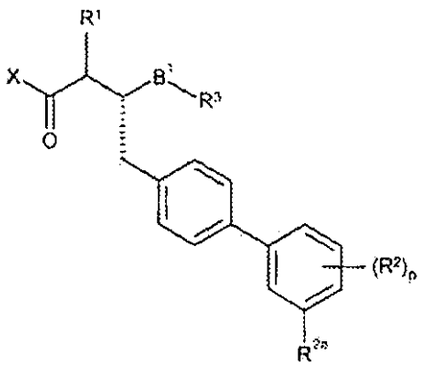
Formula IA.

or a pharmaceutically acceptable salt thereof, wherein X, R^1, R^2, B^1, R^3 and n have the definitions of Formula I or I', *supra*.

In one embodiment, the invention pertains to compounds of Formula I or I' or a pharmaceutically acceptable salt thereof, wherein n is 1, 2, 3, 4 or 5; R^2 is halo and is attached to the meta position and the other optional R^2 groups are independently C_{1-7}alkyl, NO_2, CN, halo, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, halo-C_{1-7}alkyl, NR^bR^c, C_{6-10}aryl, heteroaryl or heterocyclyl. This embodiment is illustrated by compounds of Formulae IB and IC:



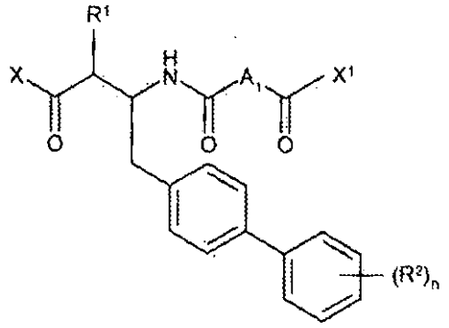
Formula IB



Formula IC

or a pharmaceutically acceptable salt thereof, wherein X, R^1, R^2, B^1, R^3 have the definitions of Formula I or I', *supra*; p is 0, 1, 2, 3 or 4 and R^{2a} is halo.

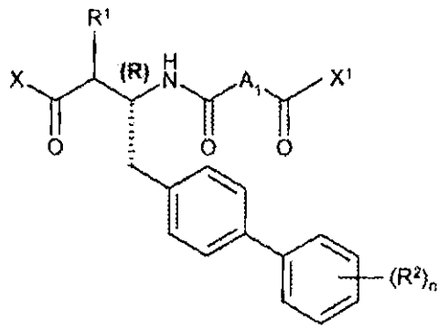
Certain compounds of Formula I or I' include compounds of Formula II:



Formula II

or a pharmaceutically acceptable salt thereof, wherein X, X^1, A^1, R^1, R^2 and n have the definitions of Formula I or I', *supra*.

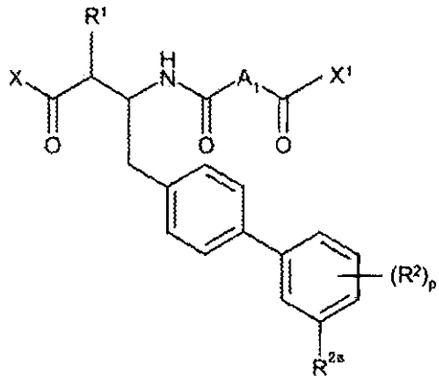
In a further embodiment, the invention pertains to compounds of Formula II wherein the stereochemistry of the carbon bearing the biphenyl groups is (R). This embodiment is illustrated by compounds of Formula IIA:



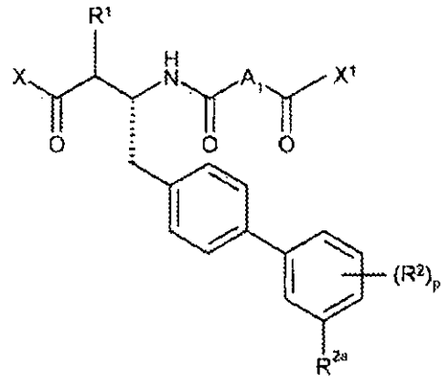
Formula IIA

or a pharmaceutically acceptable salt thereof, wherein X, X^1, A^1, R^1, R^2 and n have the definitions of Formula I or I', *supra*.

Certain compounds of Formula I, I' or II include compounds of Formula IIB or IIC:



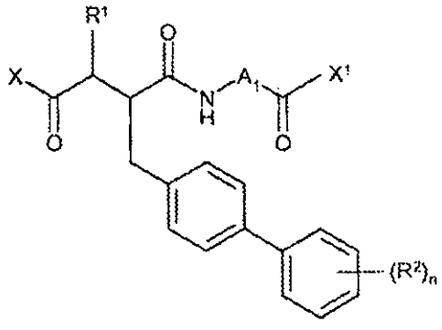
Formula IIB



Formula IIC

or a pharmaceutically acceptable salt thereof, wherein X, X^1, A^1, R^1, R^2 have the definitions of Formula I or I', *supra*; p is 0, 1, 2, 3 or 4 and R^{2a} is halo.

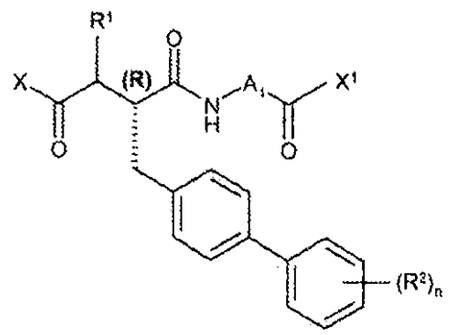
Certains compounds of Formula I or I' include compounds of Formula III:



Formula III

or a pharmaceutically acceptable salt thereof, wherein X, X^1, A^1, R^1, R^2 and n have the definitions of Formula I or I', *supra*.

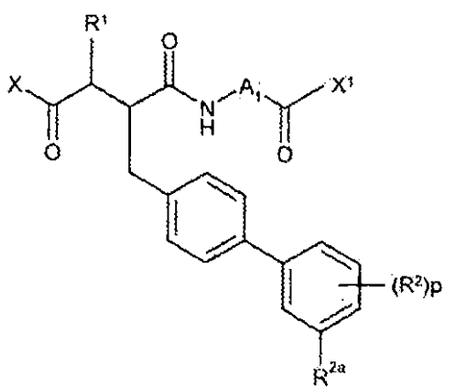
In a further embodiment, the invention pertains to compounds of Formula III wherein the stereochemistry of the carbon bearing the biphenyl groups is (R). This embodiment is illustrated by compounds of Formula IIIA:



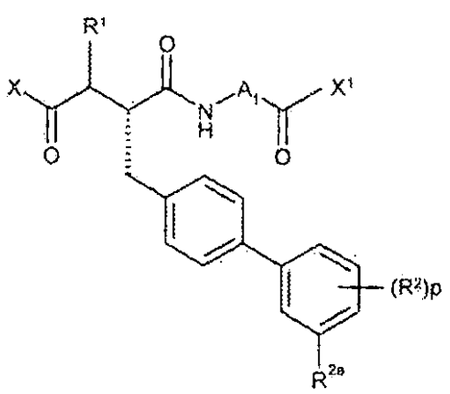
Formula IIIA

or a pharmaceutically acceptable salt thereof, wherein X, X^1, A^1, R^1, R^2 and n have the definitions of Formula I or I', *supra*.

Certain compounds of Formula III include compounds of Formula IIIB or IIIC:



Formula IIIB



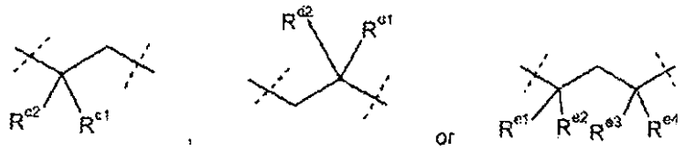
Formula IIIC

or a pharmaceutically acceptable salt thereof, wherein X, X^1, A^1, R^1, R^2 have the definitions of Formula I or I', *supra*; p is 0, 1, 2, 3 or 4 and R^{2a} is halo.

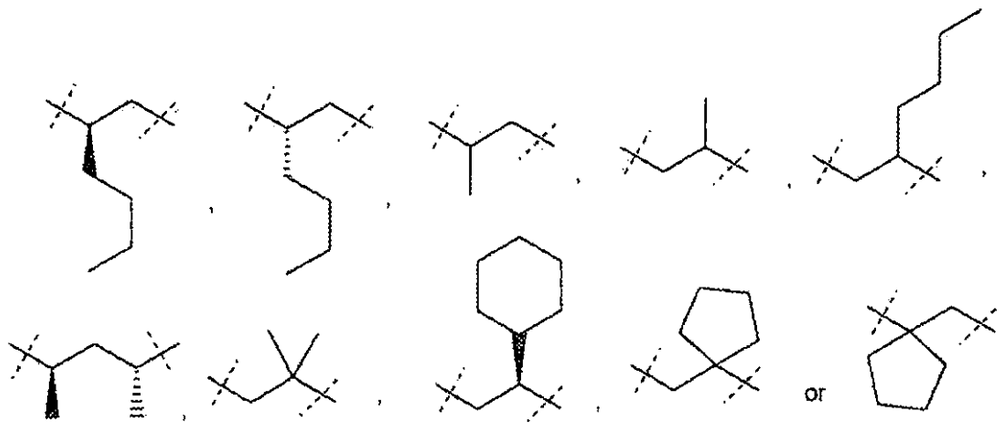
In another embodiment the invention provides a compound according to anyone of formulae I', I to IC, II to IIC and III to IIIC or of any classes and subclasses described herein, or a pharmaceutically acceptable salt or solvate thereof, wherein A^1 is a linear C_{1-7}alkylene, which is optionally substituted with one or more substituents independently selected from the

group consisting of halo, C_{1-7}alkoxy, hydroxy, O-acetate and C_{3-7}cycloalkyl; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl.

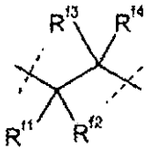
A further embodiment include compounds according to anyone of Formulae I', I to IC, II to IIC and III to IIIC or of any classes and subclasses described herein, or a pharmaceutically acceptable salt thereof, wherein A^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or A^1 has the following formulae:



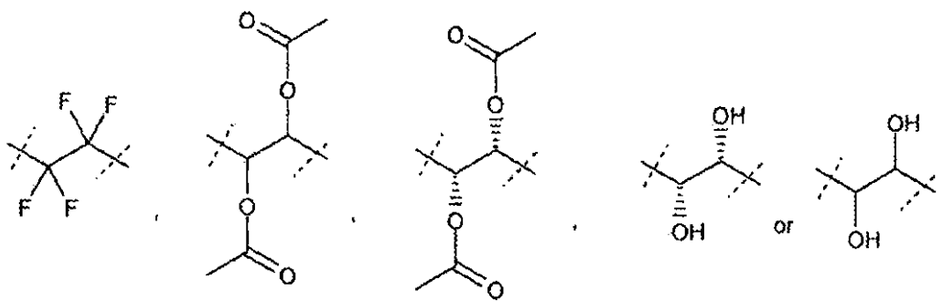
in which R^{c1}, R^{c2}, R^{d1}, R^{d2}, R^{e1}, R^{e2}, R^{e3} and R^{e4} are independently H, halo, C_{3-7}cycloalkyl, or C_{1-7}alkyl; and alternatively R^{c1} and R^{c2} or R^{d1} and R^{d2} can form together with the atoms to which they are attached a C_{3-7}cycloalkyl. In one aspect of this embodiment, A^1 is one of the following:



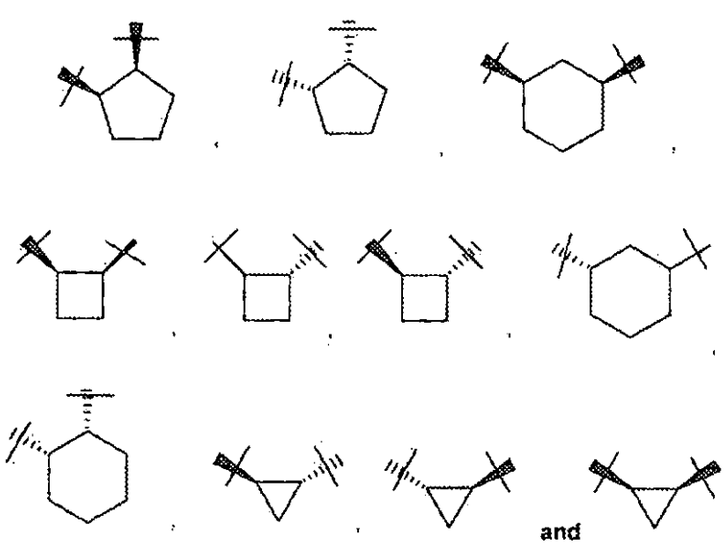
Yet another further embodiment includes compounds according to anyone of Formulae I', I to IC, II to IIC and III to IIIC or of any classes and subclasses described herein, or a pharmaceutically acceptable salt thereof, wherein A^1 has the following formulae:



in which R^{f1}, R^{f2}, R^{f3} and R^{f4} are independently H, halo, O-acetate or C_{1-7}alkyl. In a further embodiment, A^1 is one of the following:



In yet another embodiment, the invention provides a compound according to anyone of of Formulae I', I to IC, II to IIC and III to IIIC or of any classes and subclasses described herein, or a pharmaceutically acceptable salt or solvate thereof, wherein A^1 is a C_{3-7}cycloalkyl. Examples of this embodiment are compounds of anyone of Formulae I', I to IC, II to IIC and III to IIIC, wherein A1 is selected from the following:

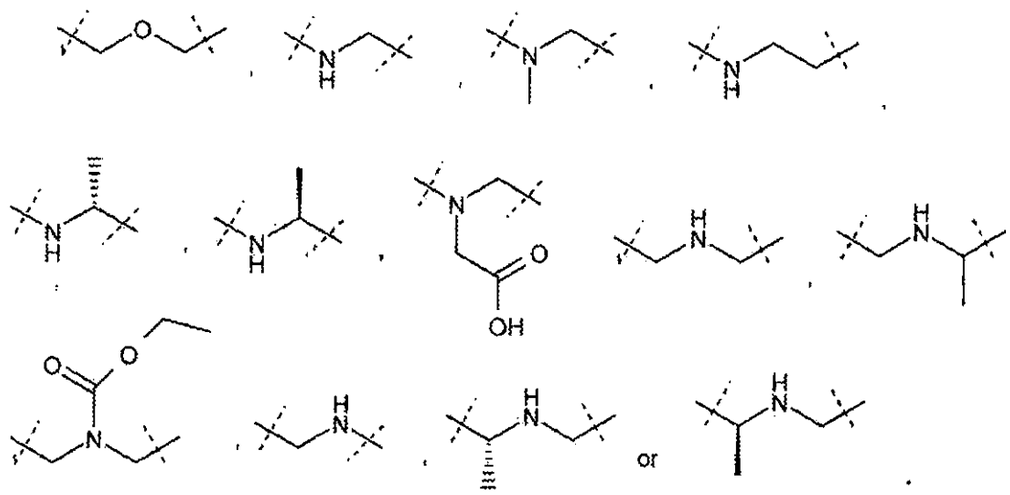


and

In yet another embodiment, the invention provides a compound according to anyone of of Formulae I', I to IC, II to IIC and III to IIIC or of any classes and subclasses described herein, or a pharmaceutically acceptable salt or solvate thereof, wherein A^1 is a linear or branched C_{2-7}alkenylene. An example of C_{2-7}alkenylene is trans CH=CH.

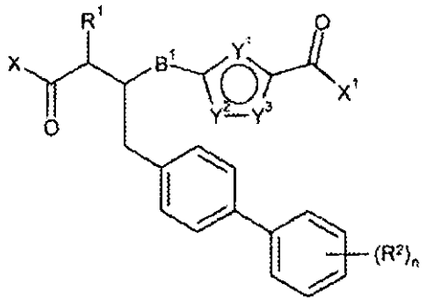
In yet another embodiment, the invention provides a compound according to anyone of of Formulae I', I to IC, II to IIC and III to IIIC or of any classes and subclasses described herein, or a pharmaceutically acceptable salt or solvate thereof, wherein A^1 is a linear C_{1-4}

alkylene wherein one or more carbon atom(s) is/are replaced with an heteroatom selected from O, NR^c; and A^1 is optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{1-7}alkyl; in which R^c for each occurrence is independenently H, C_{1-7}alkyl, -C(O)O C_{1-7}alkyl or $CH_2C(O)OH$. One further embodiment includes compounds of Formulae I', I to IC, II to IIC and III to IIIC wherein A^1 is one of the following:



In yet another embodiment, the invention provides a compound according to anyone of of Formulae I', I to IC, II to IIC and III to IIIC or of any classes and subclasses described herein, or a pharmaceutically acceptable salt or solvate thereof, wherein A^1 is optionally substituted phenyl or heteroaryl, wherein optional substituents are defined as in Formula I or I'.

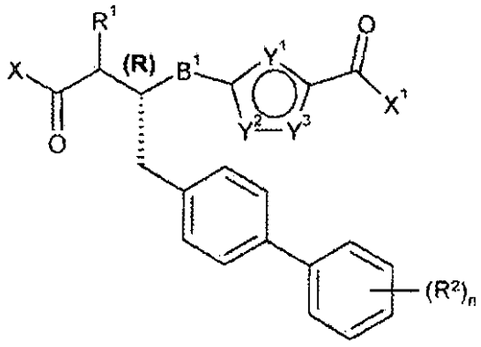
Certain compounds of the above embodiment include compounds according to anyone of Formula I', I to IC, II to IIC and III to IIIC or a pharmaceutically acceptable salt thereof, wherein A^1 is a 5-membered ring heteroaryl. This embodiment is illustrated by compounds of Formula IV:



Formula IV

or a pharmaceutically acceptable salt thereof, wherein X, X^1, B^1, R^1, R^2 and n have the definitions of Formula I or I', *supra* and and Y^1, Y^2 and Y^3 are independently N, NH, S, O or CH and form together with the ring atoms to which they are attached a 5-membered heteroaryl ring.

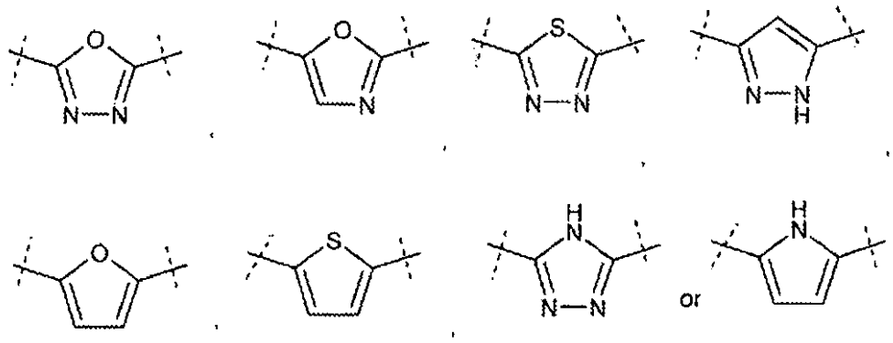
In one aspect of this embodiment, the invention pertains to compounds of Formula IVA:

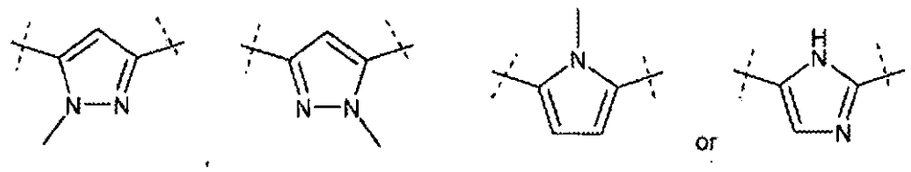


Formula IVA

or a pharmaceutically acceptable salt thereof, wherein X, X^1, B^1, R^1, R^2, Y^1, Y^2, Y^3 and n have the definitions of Formulae I, I' or IV, *supra*.

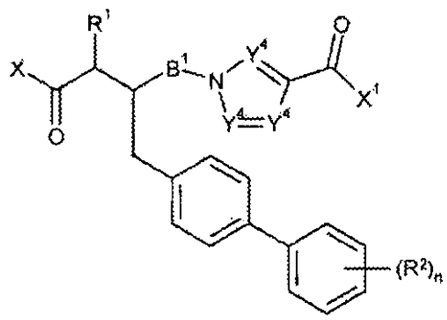
In one aspect of this embodiment, Y^1, Y^2 and Y^3 form together with the ring atoms to which they are attached a 5-membered heteroaryl ring selected from furan, thiophene, pyrrole, pyrazole, oxazole, thiazole, oxadiazole, thiadiazole, and triazole. One further embodiment includes compounds of Formula IV or VIA, or a pharmaceutically acceptable salt thereof, wherein the 5-membered heteroaryl is one of the following:



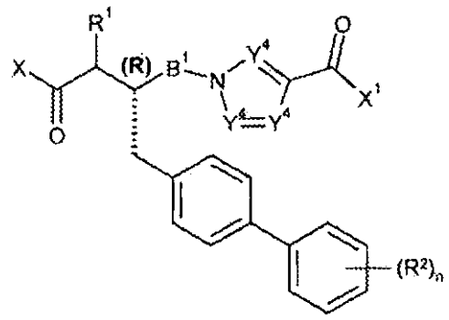


In a further embodiment, the invention pertains to compounds of Formula IV or IVA wherein n is 1, 2, 3, 4 or 5; R^2 is halo in the meta position and the other optional R^2 groups are independently C_{1-7}alkyl, NO_2, CN, halo, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, halo-C_{1-7}alkyl, NR^bR^c, C_{6-10}aryl, heteroaryl or heterocyclyl.

In yet another aspect of the above embodiment, the invention pertains to compounds of Formula I', I to IC, II to IIC or III to IIIC, or a pharmaceutically acceptable salt thereof, wherein A^1 is a 5-membered ring heteroaryl attached to the amide B^1 at a nitrogen atom. This embodiment is illustrated by compounds of Formulae V or VA:



Formula V

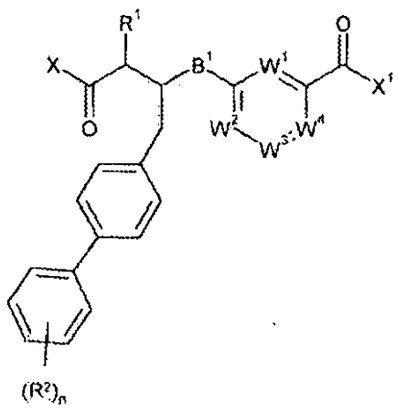


Formula VA

or a pharmaceutically acceptable salt thereof, wherein X, X^1, B^1, R^1, R^2 and n have the definitions of Formula I or I', *supra* and each Y^4 are independently N, S, O or CH. In a further embodiment, the invention pertains to compounds of Formula V or VA wherein n is 1, 2, 3, 4 or 5; R^2 is halo in the meta position and the other optional R^2 groups are independently C_{1-7}alkyl, NO_2, CN, halo, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, halo-C_{1-7}alkyl, NR^bR^c, C_{6-10}aryl, heteroaryl or heterocyclyl.

In yet another aspect of the above embodiment the invention provides a compound according to anyone of Formulae I', I to IC, II to IIC and III to IIIC or of any classes and subclasses described herein, or a pharmaceutically acceptable salt or solvate thereof, wherein A^1 is a phenyl or a 6-membered ring heteroaryl in which phenyl and heteroaryl are optionally substituted with C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, NR^aR^b, $-OCH_2CO_2H$, or $-OCH_2C(O)NH_2$. One aspect of this embodiment include compounds

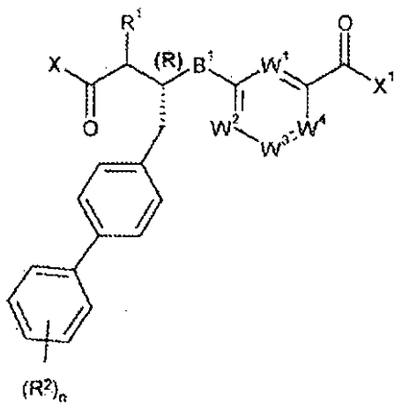
according to anyone of Formulae I', I to IC, II to IIC and III to IIIC, or pharmaceutically acceptable salt thereof, wherein A^1 is connected to the amide B^1 and to the $C(O)X^1$ moieties in a para arrangement. Another aspect of this embodiment include compounds according to anyone of Formula I', I to IC, II to IIC and III to IIIC wherein A^1 is connected to the amide B^1 and to the $C(O)X^1$ moieties in a meta arrangement. Compounds of this embodiment include compounds of Formula VI:



Formula VI

or a pharmaceutically acceptable salt thereof, wherein X, X^1, B^1, R^1, R^2 and n have the definitions of Formula I or I', *supra* and W^1, W^2, W^3 and W^4 are independently N or CR^e, in which each R^e is independently H, C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, $-NR^aRb$, $-OCH_2CO_2H$ or $-OCH_2C(O)NH_2$. In one aspect of this embodiment A^1 is phenyl, pyridine or pyrimidine.

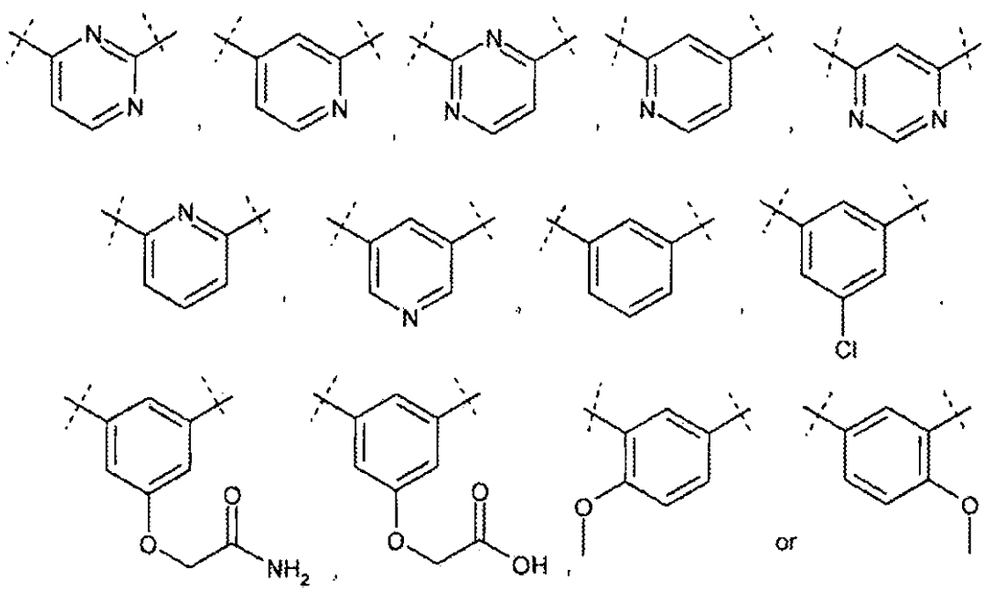
In a further embodiment, the invention pertains to compounds of Formula VIA:



Formula VIA

or a pharmaceutically acceptable salt thereof, wherein X, X^1, B^1, R^1, R^2, W^1, W^2, W^3 and W^4 and n have the definitions of Formulae I, I' or VI, *supra*.

One further embodiment includes compounds of Formula VI or VIA, or a pharmaceutically acceptable salt thereof, wherein A^1 is one of the following:

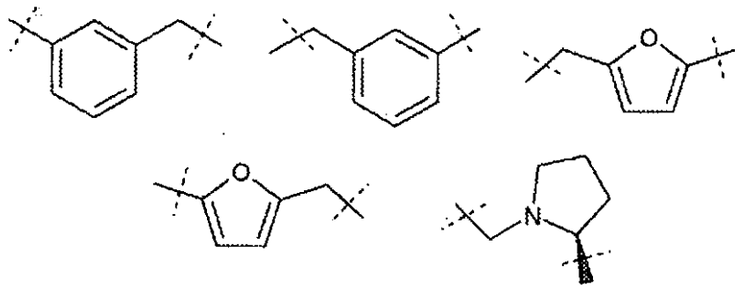


In a further embodiment, the invention pertains to compounds of Formula VI or VIA, or a pharmaceutically acceptable salt thereof, wherein n is 1, 2, 3, 4 or 5; R^2 is halo in the meta position and the other optional R^2 groups are independently C_{1-7}alkyl, NO_2, CN, halo, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, halo-C_{1-7}alkyl, NR^bR^c, C_{6-10}aryl, heteroaryl or heterocyclyl.

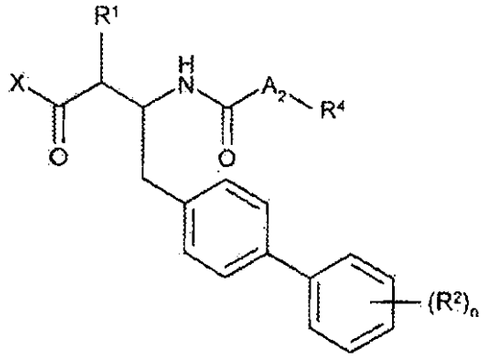
In one aspect of the previous embodiment, the invention pertains to compounds according to anyone of Formulae I', I to IC, IV to IVC, V to VC and VI to VIC, or pharmaceutically acceptable salt thereof, wherein B^1 is -C(O)NH-. In another embodiment, B^1 is -NHC(O)-.

Certain compounds of the above embodiment include compounds according to anyone of Formulae I', I to IC, II to IIC and III to IIIC, or a pharmaceutically acceptable salt thereof, wherein A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, -C_{6-10}aryl-C_{1-4}-alkylene-, -heteroaryl-C_{1-4}alkylene or –heterocyclyl-C_{1-4}alkylene-. In one aspect of this embodiment, A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein the alkylene portion is attached to B^1 amide group and the aryl, heteroaryl or heterocyclyl moities are attached to $C(O)X^1$. In another aspect of this embodiment, A^1 is –CH_2-phenyl- or -phenyl-CH_2-. In another aspect of this embodiment, A^1

is $-CH_2$-heteroaryl or -heteroaryl-CH_2-. In a further embodiment, A^1 is $-CH_2$-heterocyclyl or -heterocyclyl-CH_2-. Representative examples of A^1 are the following:

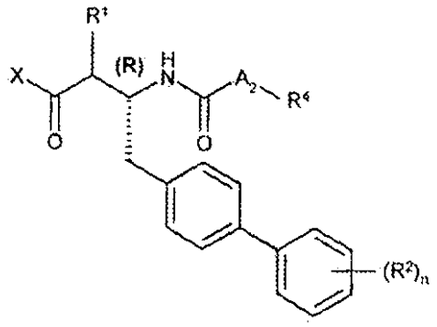


Certain compounds of Formula I or I' include compounds of Formula VII:



Formula VII

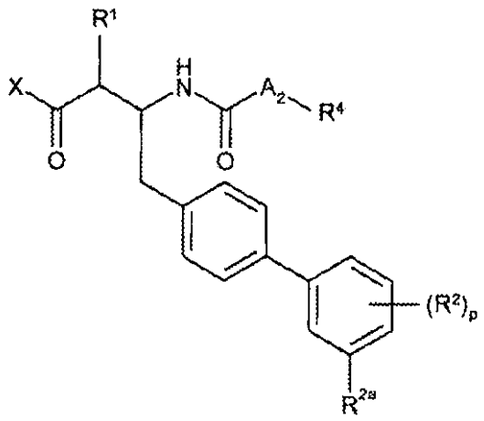
or a pharmaceutically acceptable salt thereof, wherein X, A^2, R^1, R^2, R^4 and n have the definitions of Formula I or I', *supra*. A further embodiment includes compounds of Formula VIIA:



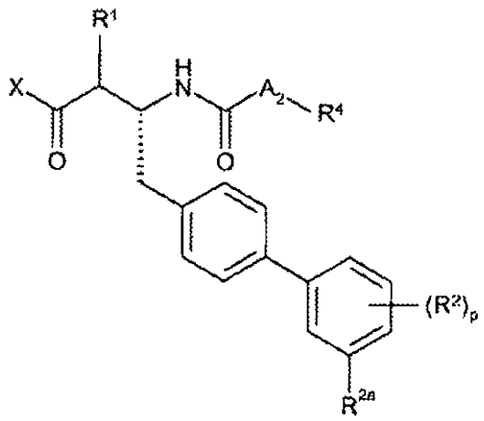
Formula VIIA

or a pharmaceutically acceptable salt thereof, wherein X, A^2, R^1, R^2, R^4 and n have the definitions of Formula I or I', *supra*.

Certain compounds of Formula VII or VIIA have the formula VIIB or VIIC:



Formula VIIB



Formula VIIC

or a pharmaceutically acceptable salt thereof, wherein X, A^2, R^1, R^2, R^4 have the definitions of Formula I or I', *supra*; p is 0, 1, 2, 3 or 4 and R^{2a} is halo.

A further aspect of this embodiment include compounds according to anyone of Formulae VII to VIIC, or a pharmaceutically acceptable salt therof, wherein A^2 is $(CH_2)_p$ and p is 0, 1, 2, 3. In one aspect of this embodiment p is 0, therefore A^2 is a bond. In another aspect of this embodiment A^2 is CH_2 or CH_2-CH_2.

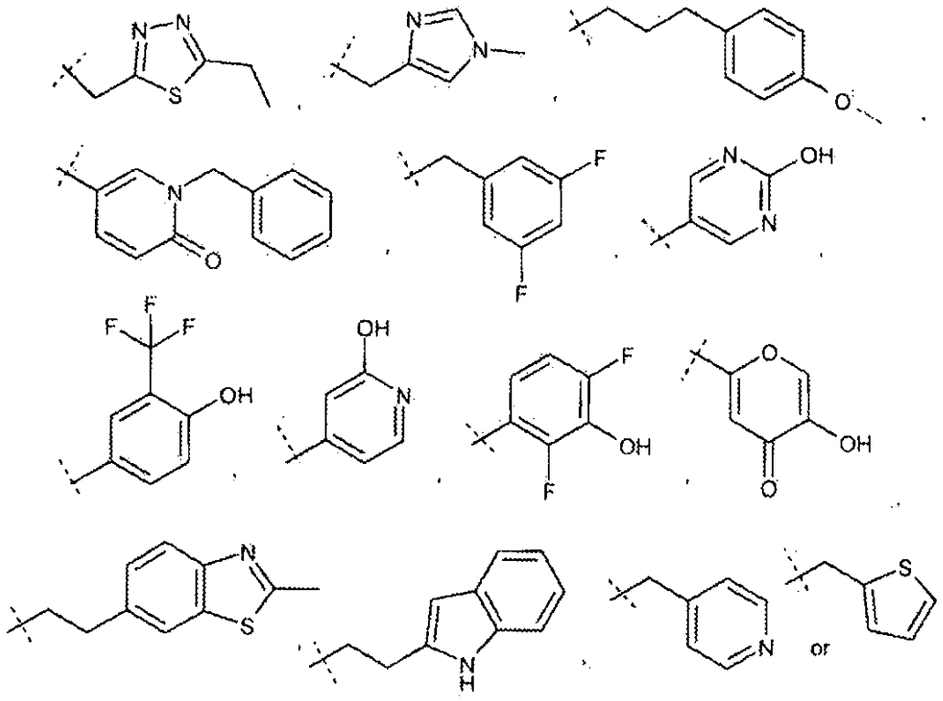
In another aspect of this embodiment the invention provide compounds according to anyone of Formulae VII to VIIC, or a pharmaceutically acceptable salt thereof, wherein R^4 is optionally substituted C_{6-10}aryl. Representative examples of aryl are benzoimidazolone, benzoisothiazolone or phenyl. In one further aspect of this embodiment, R^4 is phenyl. Substituents on the phenyl ring include for example, halo (*e.g.* F, Cl), hydroxy, halo-C_{1-7}alkyl (*e.g.* CF_3), -$NHS(O)_2$-C_{1-7}alkyl, heteroaryl, C_{1-7}alkoxy or C_{1-7}alkyl.

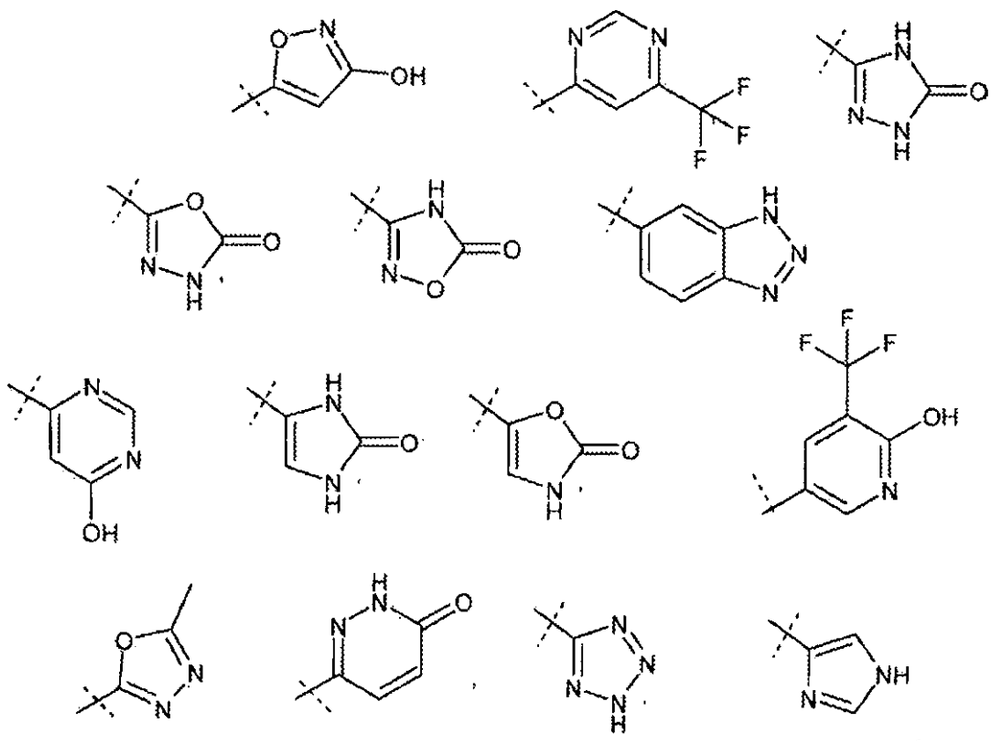
In yet another aspect of this embodiment the invention provides compounds according to anyone of Formula VII to VIIC or a pharmaceutically acceptable salt thereof, wherein R^4 is an optionally substituted bicyclic heteroaryl.

In yet another aspect of this embodiment the invention provide compounds according to anyone of Formulae VII to VIIC or a pharmaceutically acceptable salt thereof wherein R^4 is optionally substituted 5- or 6-membered heteroaryl. In one aspect of this embodiment, R^4 is a 6-membered ring heteroaryl selected from the group consisting of pyrazinyl, pyridinyl, pyrimidinyl, oxo-pyranyl (*e.g.* pyranone, optionally substituted pyran-4-one, pyran-2-one such as 3-hydroxy-pyran-4-one, 3-hydroxy-pyran-2-one), and oxo-pyridinyl (*e.g.* pyridinone, optionally substituted pyridin-4-one or pyridin-2-one such as for example 3-hydroxy-1-methyl-pyridin-4-one or 1-benzyl-pyridin-2-one), or pyrimidinone (i.e oxo-pyrimidinyl). In another aspect of this embodiment R^4 is a 5-membered ring heteroaryl selected from the group

consisting of oxazole, pyrrole, pyrazole, isooxazole, triazole, tetrazole, oxadiazole (e.g. 1-oxa-3,4-diazole, 1-oxa-2,4-diazole), oxadiazolone (*e.g.* oxadiazol-2-one), thiazole, isothiazole, thiophene, imidazole and thiadiazole. Other representative examples of R^4 are oxazolone, thiazolone, oxadiazolone, triazolone, oxazolone, imidazolone, pyrazolone. In a further embodiment, the optional substituents on C_{6-10}aryl and heteroaryl are selected from hydroxy, C_{1-7}alkyl, C_{1-7}alkoxy, halo, halo-C_{1-7}alkyl or benzyl.

In yet another aspect of the above embodiment the invention provide compounds according to anyone of Formulae VII to VIIC or a pharmaceutically acceptable salt thereof, wherein R^4 is a bicyclic heteroaryl. A further embodiment includes compounds according to anyone of Formulae VII to VIIC, or a pharmaceutically acceptable salt thereof, wherein R^4 is indole, benzothiazole or benzimidazole. Representative examples of R^4 are the following:





In yet another aspect of the above embodiment the invention provide compounds according to anyone of Formulae VII to VIIC, or a pharmaceutically acceptable salt thereof, wherein R^4 is a monocyclic saturated or partially saturated heterocyclyl, which heterocyclyl contains at least one heteroatom selected from nitrogen, sulfur and oxygen, and which heterocyclyl is optionally substituted with one or more substituents independently selected from the group consisting of oxo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl. In one particular aspect of this embodiment, R^4 is pyrrolidine or imidazolidine, wherein the heterocyclyl may be linked to the carbonyl (C(O)-A^2) moiety via a carbon or a nitrogen and the heterocyclyl is optionally substituted with oxo.

In one embodiment the invention provide compounds according to anyone of Formulae I', I to IC, II to IIC, III to IIIC, IV, IVA, V, VA, VI, VIA and VII to VIIC or a pharmaceutically acceptable salt thereof, wherein R^1 is H.

In another embodiment the invention provide compounds according to anyone of Formulae I', I to IC, II to IIC, III to IIIC, IV, IVA, V, VA, VI, VIA and VII to VIIC, or a pharmaceutically acceptable salt thereof, wherein each R^2 is independently halo, C_{1-7}alkyl, C_{1-7}alkoxy, hydroxy, halo-C_{1-7}alkyl and n is 0, 1 or 2. In a further embodiment n is 1, 2, 3, 4 or 5, R^2 is halo in the meta position and the other optional R^2 groups are independently halo,

C_{1-7}alkyl, C_{1-7}alkoxy, hydroxy or haloalkyl. In yet a further embodiment, the invention provide compounds according to anyone of Formulae I', I to IC, II to IIC, III to IIIC, IV, IVA, V, VA, VI, VIA and VII to VIIC, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2, R^2 is meta-chloro or meta-fluoro and the other optional R^2 group is halo, C_{1-7}alkyl, C_{1-7}alkoxy, hydroxy or haloalkyl.

In yet another embodiment the invention provide compounds according to anyone of Formulae I', I to IC, II to IIC, III to IIIC, I, IVA, V, VA, VI, VIA and VII to VIIC, or a pharmaceutically acceptable salt thereof, wherein X and X^1 are independently OH or -O-C_{1-7}alkyl (*e.g.* –O-ethyl, –O-methyl or –O-*n*butyl). In one particular aspect of this embodiment X and X^1 are OH. In another aspect of this embodiment, X and X^1 are independently -O-C_{1-7}alkyl in which alkyl is substituted with C_{6-10}aryl, heteroaryl, heterocyclyl, $C(O)NH_2$, C(O)NH-C_{1-6}alkyl, or $C(O)N(C_{1-6}alkyl)_2$. Representative examples of X or X^1 are –O-CH_2-$C(O)N(CH_3)_2$, -O-CH_2-CH_2-morpholine, -O-CH_2-dioxolone or -O-benzyl. In yet another aspect of this embodiment, X and X^1 are –O-C_{6-10}aryl. A representative examples of –O-C_{6-10}aryl is -O-(2,3-dihydro-1H-indene).

In another embodiment X, X^1, B^1, A^1, A^2, R^2, R^1 and R^4 groups are those defined by the X, X^1, A^1, A^2, B^1, R^2, R^1 and R^4 groups in the Examples section below.

In another embodiment individual compounds according to the invention are those listed in the Examples section below, or a pharmaceutically acceptable salt thereof.

Definition

For purposes of interpreting this specification, the following definitions will apply unless specified otherwise and whenever appropriate, terms used in the singular will also include the plural and vice versa.

As used herein, the term "alkyl" refers to a fully saturated branched or unbranched (or straight chain or linear) hydrocarbon moiety, comprising 1 to 20 carbon atoms. Preferably the alkyl comprises 1 to 7 carbon atoms, and more preferably 1 to 4 carbon atoms. Representative examples of alkyl include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl. The term "C_{1-7}alkyl" refers to a hydrocarbon having one to seven carbon atoms. Moreover, the term alkenyl includes both "unsubstituted alkyls" and "substituted alkyls". The term "alkylene" refers to a divalent alkyl radical, wherein alkyl is as previously defined.

The term "alkenyl" refers to a branched or unbranched hydrocarbon having at least one carbon-carbon double bond. The term "C_{2-7}alkenyl" refers to a hydrocarbon having two to seven carbon atoms and comprising at least one carbon-carbon double bond. Representative examples of alkenyl are vinyl, prop-1-enyl, allyl, butenyl, isopropenyl or isobutenyl. The term "alkeylene" refers to a divalent alkenyl radical, wherein alkenyl is as previously defined.

As used herein, the term "haloalkyl" refers to an alkyl as defined herein,that is substituted by one or more halo groups as defined herein. Preferably the haloalkyl can be monohaloalkyl, dihaloalkyl or polyhaloalkyl including perhaloalkyl. A monohaloalkyl can have one iodo, bromo, chloro or fluoro within the alkyl group. Dihaloalky and polyhaloalkyl groups can have two or more of the same halo atoms or a combination of different halo groups within the alkyl. Preferably, the polyhaloalkyl contains up to 12, or 10, or 8, or 6, or 4, or 3, or 2 halo groups. Representative examples of haloalkyl are fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. A perhaloalkyl refers to an alkyl having all hydrogen atoms replaced with halo atoms. The term "halo-C_{1-7}alkyl" refers to a hydrocarbon having one to seven carbon atoms and being substituted by one or more halo groups.

As used herein, the term "alkoxy" refers to alkyl-O-, wherein alkyl is defined herein above. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, hexyloxy, cyclopropyloxy-, cyclohexyloxy- and the like. Preferably, alkoxy groups have about 1-7, more preferably about 1-4 carbons.

As used herein, the term "cycloalkyl" refers to saturated or unsaturated but non-aromatic monocyclic, bicyclic or tricyclic hydrocarbon groups of 3-12 carbon atoms, preferably 3-8, or 3-7 carbon atoms. For bicyclic, and tricyclic cycloalkyl system, all rings are non-aromatic. Exemplary monocyclic hydrocarbon groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl. Exemplary bicyclic hydrocarbon groups include bornyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, bicyclo[2.2.2]octyl. Exemplary tricyclic hydrocarbon groups include adamantyl. The term "C_{3-7}cycloakyl" refers to a cyclic hydrocarbon groups having 3 to 7 carbon atoms. The term "cycloalkylalkyl" refers to an alkyl susbtituted with cycloalkyl.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6-10 carbon atoms in the ring portion. The term "aryl" also refer to a group in which the

aromatic ring is fused to a cycloalkyl ring, where the radical of attachment is on the aromatic ring or on the fused cycloalkyl ring. Representative examples of aryl are phenyl, naphthyl, hexahydroindyl, indanyl or tetrahydronaphthyl. The term "C_{6-10} aryl" refers to an aromatic hydrocarbon groups having 6 to 10 carbon atoms in the ring portion.

The term "arylalkyl" is an alkyl substituted with aryl. Representative examples of arylalkyl are benzyl or Phenyl-CH_2CH_2-. The term also includes substituted arylalkyl moiety.

The term "Heteroaryl" includes monocyclic or bicyclic heteroaryl, containing from 5-10 ring members selected from carbon atoms and 1 to 5 heteroatoms, and each heteroatoms is indepdendently selected from O, N or S wherein S and N may be oxidized to various oxidation states. For bicyclic heteroaryl system, the system is fully aromatic (i.e. all rings are aromatic).

Typical monocyclic heteroaryl groups include thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxa-2,3-diazolyl, oxa-2,4-diazolyl, oxa-2,5-diazolyl, oxa-3,4-diazolyl, thia-2,3-diazolyl, thia-2,4-diazolyl, thia-2,5-diazolyl, thia-3,4-diazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 3- or 5-1,2,4-triazolyl, 4- or 5-1,2, 3-triazolyl, tetrazolyl, 2-, 3-, or 4-pyridyl, 3- or 4-pyridazinyl, 3-, 4-, or 5-pyrazinyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl.

The term "heteroaryl" also refers to a group in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring or on the fused aryl ring. Representative examples of bicyclic heteroaryl are indolyl, isoindolyl, indazolyl, indolizinyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, quinazolinyl, quinaxalinyl, thieno[2,3-b]furanyl, furo[3,2-b]-pyranyl, 5H-pyrido[2,3-d]-o-oxazinyl, 1H-pyrazolo[4,3-d]-oxazolyl, 4H-imidazo[4,5-d] thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b] thiazolyl, imidazo[1,2-b][1,2,4]triazinyl, 7-benzo[b]thienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzoxapinyl, benzoxazinyl, 1H-pyrrolo[1,2-b][2]benzazapinyl, benzofuryl, benzothiophenyl, benzotriazolyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,2-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, pyrrolo[3,2-b]pyridinyl, imidazo[4,5-b]pyridinyl, imidazo[4,5-c]pyridinyl, pyrazolo[4,3-d]pyridinyl, pyrazolo[4,3-c]pyridinyl, pyrazolo[3,4-c]pyridinyl, pyrazolo[3,4-d]pyridinyl, pyrazolo[3,4-b]pyridinyl, imidazo[1,2-a]pyridinyl, pyrazolo[1,5-a]pyridinyl, pyrrolo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, pyrido[3,2-d]pyrimidinyl, pyrido[4,3-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrido[2,3-d]pyrimidinyl, pyrido[2,3-b]pyrazinyl, pyrido[3,4-b]pyrazinyl, pyrimido[5,4-d]pyrimidinyl, pyrazino[2,3-b]pyrazinyl, or pyrimido[4,5-d]pyrimidinyl.

When a heteroaryl moiety is substituted with hydroxy, the invention also pertains to its oxo tautomeric. For example, an oxadiazole substituted with hydroxy also includes oxo-oxadiazole or also known as oxadiazolone. The tautomerisation is represented as follow:



As used herein, the term "heterocyclyl" or "heterocyclo" refers to an optionally substituted, saturated or unsaturated non-aromatic (partially unsaturated) ring which is a 4-, 5-, 6-, or 7-membered monocyclic, and contains at least one heteroatom selected from O, S and N, where the N and S can also optionally be oxidized to various oxidation states. For bicyclic and tricyclic heterocyclyl ring system, a non-aromatic ring system is defined as being a non-fully or partially unsaturated ring system. Therefore bicyclic and tricyclic heterocyclyl ring systems includes heterocyclyl ring systems wherein one of the fused rings is aromatic but the other(s) is (are) non-aromatic. In one embodiment, heterocyclyl moiety represents a saturated monocyclic ring containing from 5-7 ring atoms and optionally containing a further heteroatom, selected from O, S or N. The heterocyclic group can be attached at a heteroatom or a carbon atom. The heterocyclyl can include fused or bridged rings as well as spirocyclic rings. Examples of heterocycles include dihydrofuranyl, dioxolanyl, dioxanyl, dithianyl, piperazinyl, pyrrolidine, dihydropyranyl, oxathiolanyl, dithiolane, oxathianyl, thiomorpholino, oxiranyl, aziridinyl, oxetanyl, oxepanyl, azetidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, morpholino, piperazinyl, azepinyl, oxapinyl, oxaazepanyl, oxathianyl, thiepanyl, azepanyl, dioxepanyl, and diazepanyl.

The term "hydroxyalkyl" refers to alkyl groups, as decribed above, in which the alkyl group is substituted with one or more hydroxy.

The term "halogen" includes fluorine, bromine, chlorine and iodine. The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus. In another embodiment, the heteroatom is nitrogen, oxygen or sulfur.

It will be noted that the structure of some of the compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from

such asymmetry (*e.g.*, all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof.

As used herein, the term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50 %

enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate,

succinate, tartrate, tosylate and trifluoroacetate salts. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*- toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. For example, any hydrogen represented by "H" in any of the formulae herein is intended to represent all isotopic forms of hydrogen (e.g. ^{1}H, ^{2}H or D, ^{3}H); any carbon represented by "C" in any of the formulae herein is intended to represent all isotopic forms of carbon (e.g. ^{11}C, ^{13}C, ^{14}C); any nitrogen represented by "N" is intended to represent all isotopic forms of nitrogen (e.g. ^{14}N, ^{15}N). Other examples of isotopes that are included in the invention include isotopes of oxygen, sulfur, phosphorous, fluorine, iodine and chlorine, such as ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I. The invention includes

various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H, ^{13}C, and ^{14}C are present. In one embodiment, the atoms in the formulae herein occur in their natural abundance. In another embodiment, one or more hydrogen atom may be enriched in ^{2}H; or/and one or more carbon atom may be enriched in ^{11}C, ^{13}C or ^{14}C; or/and one or more nitrogen may be enriched in ^{14}N. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Further, enrichment with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound according to anyone of the formulae I' and I to VIIC. The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Isotopically-enriched compounds of formulae I' or I to VIIC can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-enriched reagent in place of the non-enriched reagent previously employed

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Compounds of the invention, i.e. compounds accroding to anyone of formulae I' and I to VIIC, that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds according to anyone of formulae I' and I to VIIC by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds according to anyone of formulae I' and I to VIIC with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound according to anyone of formulae I' and I to VIIC.

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, such like materials and combinations thereof, as would be known to one of ordinary skill in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder or a disease (i) mediated by neutral endopeptidase EC 3.4. 24.11 or (ii) associated with neutral endopeptidase EC 3.4. 24.11 activity, or (iii) characterized by abnormal activity of neutral endopeptidase EC 3.4. 24.11; or (2) reducing or inhibiting the activity of neutral endopeptidase EC 3.4. 24.11; or (3) reducing or inhibiting the expression of neutral endopeptidase EC 3.4. 24.11. In another non-limiting

embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of neutral endopeptidase EC 3.4. 24.11; or at least partially reducing or inhibiting the expression of neutral endopeptidase EC 3.4. 24.11.

As used herein, the term "subject" refers to an animal. Preferably, the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In a preferred embodiment, the subject is a human.

As used herein, the term "inhibition" or "inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

As used herein, the term "a," "an," "the" and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

The term "hypertension" refers to a condition where the pressure of blood within the blood vessels is higher than normal as it circulates through the body. When the systolic pressure exceeds 150 mmHg or the diastolic pressure exceeds 90 mmHg for a sustained period of time, damage is done to the body. For example, excessive systolic pressure can rupture blood vessels anywhere, and when it occurs within the brain, a stroke results. Hypertension may also cause thickening and narrowing of the blood vessels which ultimately could lead to atherosclerosis.

The term "type 2 diabetes" including type 2 diabetes associated with hypertension refers to a disease in which the pancreas does not secrete sufficient insulin due to an impairment of pancreatic beta-cell function and/or in which there is to insensitivity to produced insulin (insulin resistance). Typically, the fasting plasma glucose is less than 126 mg/dL, while pre-diabetes is, e.g., a condition which is characterized by one of following conditions: impaired fasting glucose (110-125 mg/dL) and impaired glucose tolerance (fasting glucose levels less than 126 mg/dL and post-prandial glucose level between 140 mg/dL and 199 mg/dL). Type 2 diabetes mellitus can be associated with or without hypertension. Diabetes mellitus occurs frequently, e.g., in African American, Latino/Hispanic American, Native American, Native American, Asian American and Pacific Islanders. Markers of insulin resistance include HbA1C, HOMA IR, measuring collagen fragments, TGF-β in urine, PAI-1 and prorenin.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.* "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

Compounds of the present invention are either obtained in the free form, as a salt thereof, or as prodrug derivatives thereof.

When both a basic group and an acid group are present in the same molecule, the compounds of the present invention may also form internal salts, e.g., zwitterionic molecules.

The present invention also provides pro-drugs of the compounds of the present invention that converts *in vivo* to the compounds of the present invention. A pro-drug is an active or inactive compound that is modified chemically through *in vivo* physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a subject. The suitability and techniques involved in making and using pro-drugs are well known by those skilled in the art. Prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. See *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001). Generally, bioprecursor prodrugs are compounds, which are inactive or have low activity compared to the corresponding active drug compound that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity. Carrier prodrugs are drug compounds that contain a transport moiety, *e.g.*, that improve

uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, and any released transport moiety is acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, *e.g.*, certain polymers or other moieties, such as cyclodextrins. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement in drug formulation (*e.g.*, stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of (a) hydroxyl groups with lipophilic carboxylic acids (e.g., a carboxylic acid having at least one lipophilic moiety), or (b) carboxylic acid groups with lipophilic alcohols (e.g., an alcohol having at least one lipophilic moiety, for example aliphatic alcohols).

Exemplary prodrugs are, *e.g.*, esters of free carboxylic acids and *S*-acyl derivatives of thiols and O-acyl derivatives of alcohols or phenols, wherein acyl has a meaning as defined herein. Preferred are pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, *e.g.*, lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or di-substituted lower alkyl esters, such as the ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the α-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester and the like conventionally used in the art. In addition, amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases *in vivo* releasing the free drug and formaldehyde (Bundgaard, *J. Med. Chem.* 2503 (1989)). Moreover, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard, *Design of Prodrugs*, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

GENERAL SYNTHETIC ASPECTS

The compounds of the invention can be synthesized using the methods described in the following schemes, examples, and by using art recognized techniques. All compounds described herein are included in the invention as compounds. Compounds of the invention may be synthesized according to at least one of the methods described in schemes 1-4.

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999.

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known per se. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, *e.g.* the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, *e.g.* by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, *e.g.* a free carboxy group and a free amino group, may be formed, *e.g.* by the neutralisation of salts, such as acid addition salts, to the isoelectric point, *e.g.* with weak bases, or by treatment with ion exchangers.

Salts can be converted in customary manner into the free compounds; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known per se into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or

chromatographic separation, for example over silica gel or by *e.g.* medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, *e.g.* using chromatographic methods, distribution methods, (re-) crystallization, and the like.

The following applies in general to all processes mentioned herein before and hereinafter.

All the above-mentioned process steps can be carried out under reaction conditions that are known per se, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, *e.g.* in the H+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 °C to about 190 °C, including, for example, from approximately -80 °C to approximately 150 °C, for example at from -80 to -60 °C, at room temperature, at from -20 to 40 °C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example analogously to the methods described under "Additional process steps".

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or *N*-methylpyrrolidin-2-

one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, methycyclohexane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21).

The compounds of the invention according to anyone of formulae I' and I to VIIC can be prepared by the procedure described in the following sections.

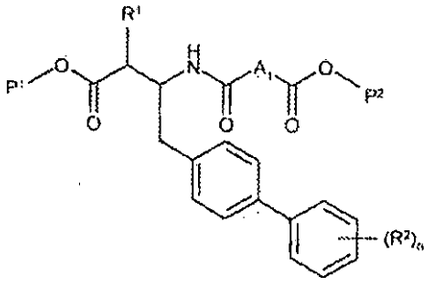
Abbreviations:

ATP: adenosine 5'-triphosphate	AS: Aldosterone Synthase
Alloc: allyloxycarbonyl	BOC: tertiary butyl carboxy
BOP:benzotriazole1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate	BINAP: racemic 2,2'-bis(diphenyl phosphino)-1,1'-binaphthyl
br: broad	bs: broad singlet
Ac: Acetyl	Atm: atmosphere
Aq: aqueous	calcd: calculated
Bn: benzyl	Cbz: benzyloxycarbonyl
Bu, i-bu and t-Bu: butyl, isobutyl and t-butyl	Pr and i-Pr: propyl and isopropyl
CDI: 1, 1'-carbonyldiimidazole	COD: 1,5-cyclooctadiene
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene	DCC: 1,3-dicyclohexylcarbodiimide
DIAD: diisopropyl azodicarboxylate	DAST: (diethylamino)sulfur

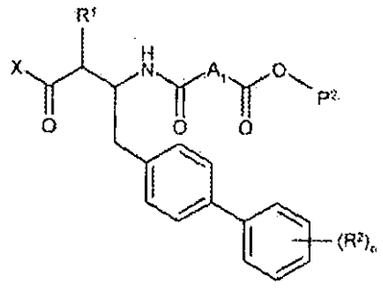
	trifluoride
d: doublet dd: doublet of doublets	DCM: dichloromethane
DIEA: diethylisopropylamine	DME: 1,4-dimethoxyethane
DMF: *N,N*-dimethylformamide	DMSO: dimethylsulfoxide
DIPEA: N,N-diisopropylethylamine	DMAP: N,N-dimethylaminopyridine
Dppb: 1,2-bis(diphenylphosphino)butane	Dppe: 1,2-bis(diphenylphosphino) ethane
DAD: diode array detector	DTT: dithiothreitol
DPPA: diphenylphosphorylazide	EDCI, EDIC: N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
EDTA: ethylenediamine tetraacetic acid	ESI: electrospray ionization
Et and EtOAc: ethyl and ethyl acetate	EDC: N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
HATU: *O*-(7-azobenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate	HOBt: 1-hydroxy-7-azabenzotriazole
HPLC: high pressure liquid chromatography	LC and LCMS: liquid chromatography and liquid chromatography and mass spectrometry
H: Hour(s)	HOAt: 1-hydroxy-7-azabezotriazole
IR: infrared	LDA: lithium diisopropylamide
KHMDS: potassium bis(trimethylsilyl)amide	LHMDS: lithium bis(trimethylsilyl)amide
LTA: lead tetraacetate	NHMDS: sodium bis(trimethylsilyl)amide
MeOD: methanol-d4	MeOH: methanol
MS: mass spectrometry	m: multiplet
min: minutes	m/z: mass to charge ratio
Ms: mesyl	Me: methyl
M and mM: Molar and millimolar	Mg: milligram
n.d.: not determined	NMR: nuclear magnetic resonance

ppm: parts per million	Pr and iPr: propyl and isopropyl
Ph: Phenyl	Pd/C: Palladium on Carbom
PyBOP: benzotriazol-1-yloxy Tripyrrolidinophosphoniumhexafluorophosphate	RT: room temperature
PIDA: iodobenzene bis(trifluoroacetate)	PIFA: iodobenzene diacetate
PS: polymer supported	RP: reverse phase
s: singlet adn t: triplet	Ts tosyl
TFA: trifluoroacetic acid	THF: tetrahydrofuran
Tf: triflate	tBu: tert-butyl
TLC: thin layer chromatography	Tris·HCl: aminotris(hydroxymethyl) methane hydrochloride
µL, mL and L: microlitre, millilitre and litre	TMS: Trimethylsilyl
WSC: water soluble carbodiimide (N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide	UV: ultraviolet

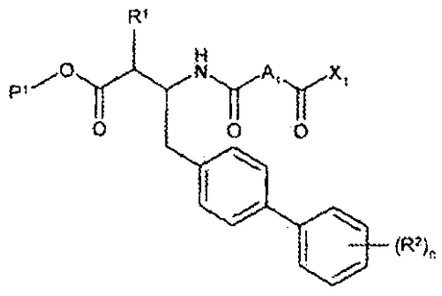
The compounds of the invention of formula II can be prepared by hydrolysis of intermediates **A** to **C** wherein X, X^1, A^1, R^1, R^2 and n have the definition of Formula I or I', *supra*; and P^1 and P^2 are appropriate protecting groups selected from, but not limited to, methyl, ethyl, isopropyl, tert-butyl, methoxybenzyl or benzyl.



Intermediate A

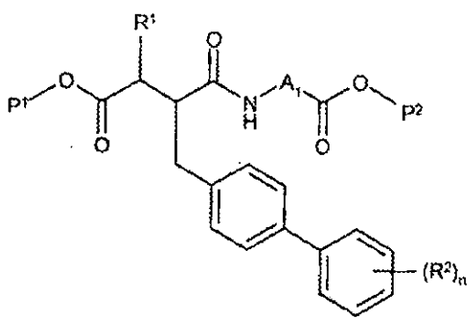


Intermediate B

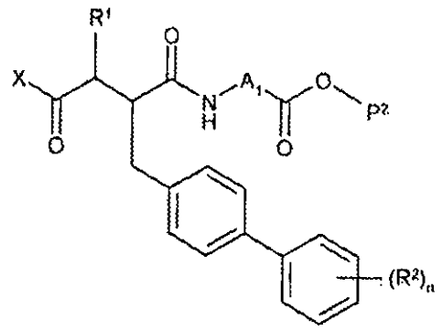


Intermediate C

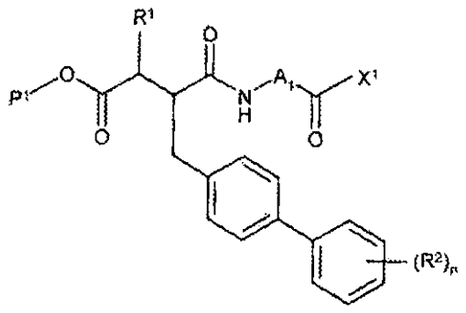
The compounds of the invention of formula III can be prepared by hydrolysis of intermediate **D**, **E** or **F** wherein X, X^1, A^1, R^1, R^2 and n have the definition of Formula I or I', *supra*; and P^1 and P^2 can be appropriate protecting groups selected from, but not limited to, methyl, ethyl, isopropyl, *tert*-butyl, methoxybenzyl or benzyl.



Intermediate D

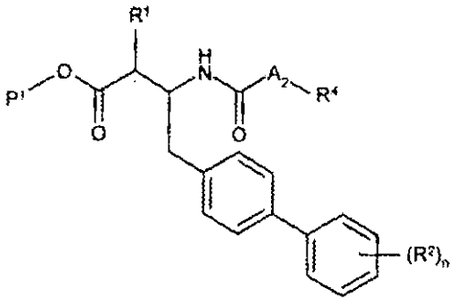


Intermediate E



Intermediate F

The compounds of the invention of formula VII can be prepared by hydrolysis of intermediate **G** wherein A^2, R^1, R^2, R^4 and n have the definition of Formula I or I', *supra*; and P^1 can be appropriate protecting group selected from, but not limited to, methyl, ethyl, isopropyl, *tert*-butyl, methoxybenzyl or benzyl.

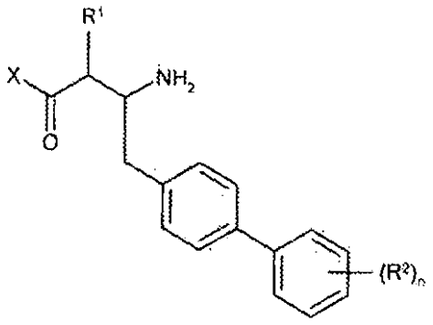


Intermediate G

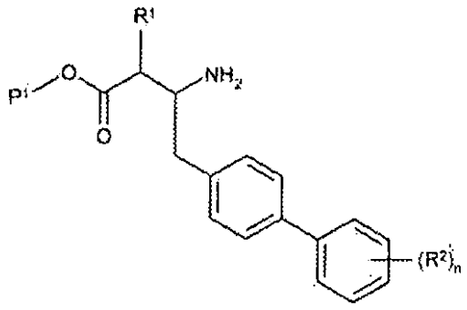
Standard methods can be applied for the hydrolysis of Intermeidates A to G using a base selected from, but not limited to, NaOH, KOH or LiOH, or an acid selected from, but not

limited to, TFA or HCl. When P^1 or P^2 is benzyl or methoxybenzyl, preferable method of deprotection is hydrogenation in the presence of a catalyst such as, but not limited to, palladium-on-carbon under hydrogen.

The intermediate **A**, **B**, **C** or **G** can be prepared using the following process comprising: condensing an intermediate **H** or **I** wherein X, P^1, R^1, R^2 and n are as previously described:

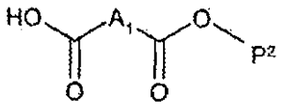


Intermediate H

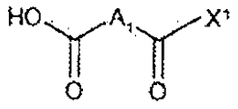


Intermediate I

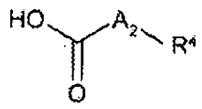
with an intermediate **J**, **K** or **L** wherein X^1, A^1, A^2, R^4 and P^2 are previously described.



Intermediate J



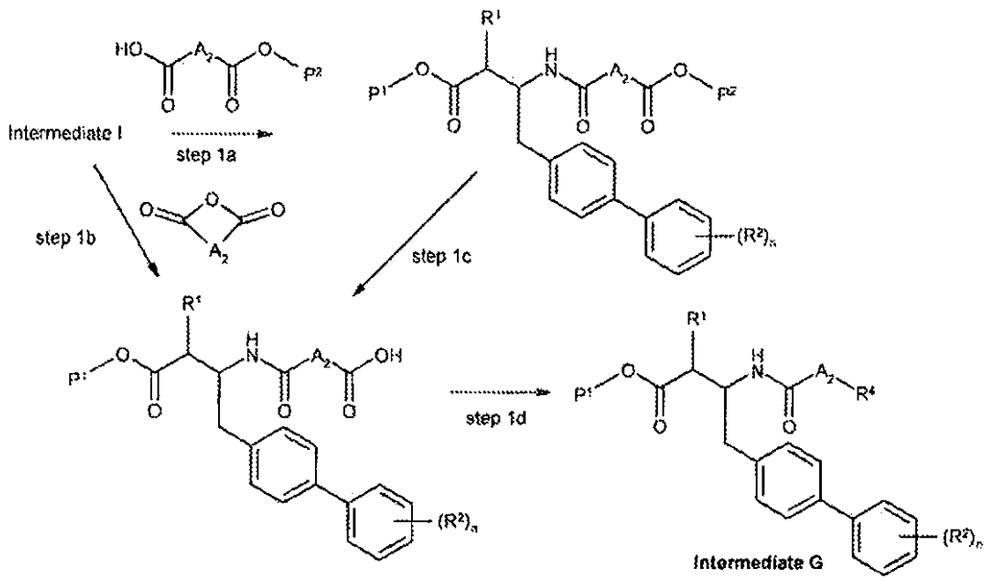
Intermediate K



Intermediate L

Known condensation methods may be applied including, but not limited to, conversion of the intermediate **J**, **K** or **L** to their corresponding acid halide, using reagents such as thionyl chloride or oxalyl chloride, or conversion of intermediate **J**, **K** or **L** to mixed anhydride using reagents such as ClC(O)O-isobutyl or 2,4,6-trichlorobenzoyl chloride followed by reaction of the acid halide or mixed anhydride with the intermediate **H** or **I** in a presence or absence of a base such as tertiary amine (e.g. triethylamine, DIPEA, or *N*-methylmorpholine) or pyridine derivative (e.g. pyridine, 4-(dimethylamino)pyridine, or 4-pyrrolidinopyridine). Alternatively, the intermediate **J**, **K**, or **L** can be coupled with H or I using coupling reagents such as DCC, EDCI, PyBOP or BOP in presence or absence of a reagent such as 1-hydroxybenazotriazole, 1-hydroxy-7-azabenzotriazole or pentafluorophenol.

Intermediate **G** wherein R^4 is a tetrazole can be synthesized according to Scheme 1:

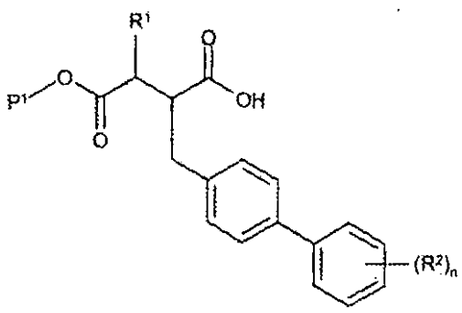


Scheme 1

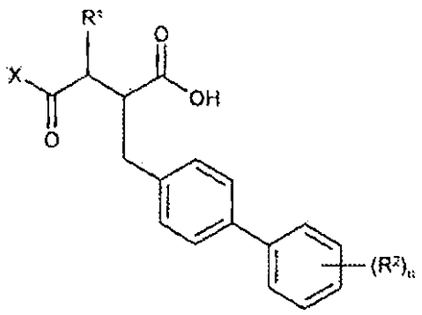
wherein A^2, R^1, R^2, R^4, P^1, P^2 and n are as previously defined above.

In step 1a, intermediate **I** is reacted with an appropriate carboxylic acid using standard coupling reagents selected from, but not limited to, DCC, EDCI, PyBOP or BOP in presence or absence of a reagent such as 1-hydroxybenazotriazole, 1-hydroxy-7-azabenzotriazole or pentafluorophenol; follwoed by removal of P^2 protecting group in step 1c using a base selected from, but not limited to, NaOH, KOH or LiOH, or an acid selected from, but not limited to, TFA or HCl, or hydrogenation with a catalyst such as, but not limited to, palladium-on-carbon under hydrogen. Alternatively, intermediate I is reacted with an appropriate anhydride in the presence of a base selected from, but not limited to, pyridine, triethylamine or diisopropylethylamine (step 1b); followed by conversion of the carboxylic acid into a tetrazole (step 1b) using similar method as described in *Journal of Medicinal Chemistry* 1998, 41, 1513.

The intermediate **D, E** or **F** can be prepared using the following process comprising: condensing an intermediate **M** wherein X, P^1, R^1, R^2 and n are as defined above;

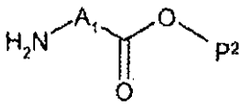


Intermediate M

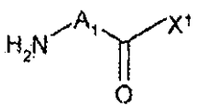


Intermediate N

with an intermediate **Q** or **S** wherein X^1, A^1 and P^2 have the meaning as defined above.



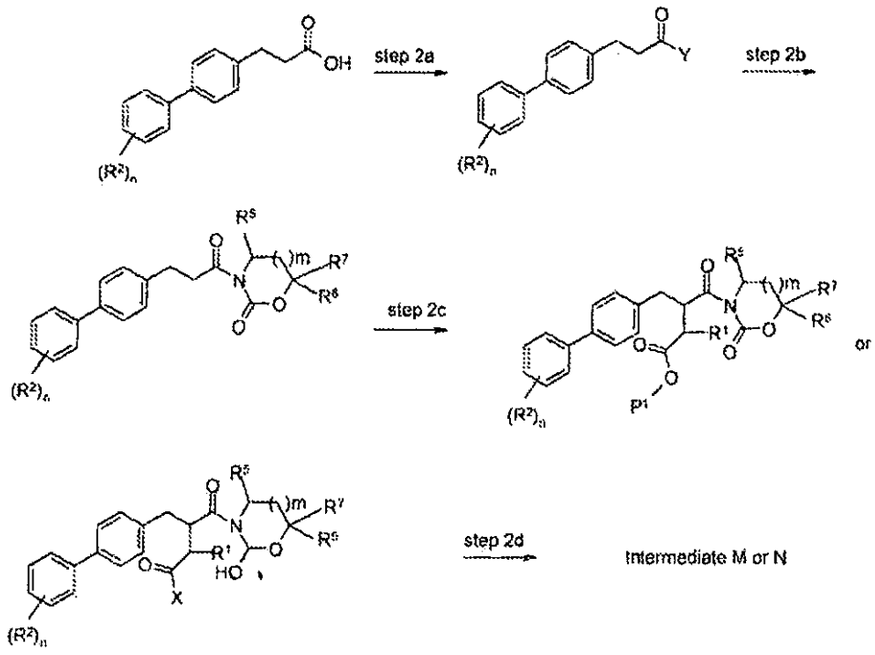
Intermediate Q



Intermediate S

Known condensation methods may be applied including, but not limited to, conversion of the intermediate **M** or **N** to acid halide, using reagents such as thionyl chloride or oxalyl chloride, or conversion of intermediate **M** or **N** to mixed anhydride using reagents such as ClC(O)O-isobutyl or 2,4,6-trichlorobenzoyl chloride followed by reaction of the acid chloride or mixed anhydride with the intermediate **Q** or **S** in a presence or absence of a base such as tertiary amine (e.g. triethylamine, DIPEA, or *N*-methylmorpholine) or pyridine derivative (e.g. pyridine, 4-(dimethylamino)pyridine, or 4-pyrrolidinopyridine); Alternatively, the intermediate M or N can be coupled with the intermediate **Q** or **S** using a reagent such as DCC, EDCI, PyBOP or BOP in presence or absence of a reagent such as 1-hydroxybenazotriazole, 1-hydroxy-7-azabenzotriazole or pentafluorophenol.

The intermediate **M** or **N** can be prepared according to the following general procedures described in Scheme 2:



Scheme 2

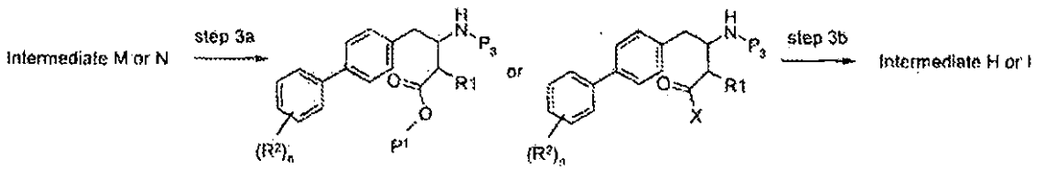
wherein R^1, R^2, X and n are as defined above and wherein m = 0 or 1; P^1 is a protecting group selected from, but not limited to, hydrogen, methyl, ethyl, propyl, *tert*-butyl, methoxymethyl, *tert*-butyldimethylsilyl, tetrahydrofuranyl, benzyl, allyl or phenyl; R^5 is for example hydrogen, methyl, ethyl, isopropyl, benzyl or phenyl; R^6 and R^7 are independently hydrogen, methyl, ethyl, isopropyl, benzyl or phenyl. Y is selected from, but not limited to, chloro, bromo, iodo, benzotriazoloxy, pyridinium, *N,N*-dimethylaminopyridinium, pentafluorophenoxy, phenoxy, 4-chlorophenoxy, $-OCO_2Me$, $-OCO_2Et$, *tert*-butoxycarbonyl or -OCC(O)O-isobutyl.

In step (2a), standard methods can be applied to prepare the corresponding acid halide, such as the use of thionyl chloride, oxalyl chloride; or standard methods to prepare the mixed anhydride or the acyl pyridinium cation can be applied, such as the use of pivaloyl chloride with a tertiary amine (e.g. triethylamine, DIPEA, *N*-methylmorpholine) in the presence or absence of a pyridine derivative (e.g. pyridine, 4-(dimethylamino)pyridine, 4-pyrrolidinopyridine), 2,4,6-trichlorobenzoyl chloride with a tertiary amine (e.g. triethylamine, DIPEA, *N*-methylmorpholine) in the presence or absence of a pyridine derivative (e.g. pyridine, 4-(dimethylamino)pyridine, 4-pyrrolidinopyridine), or ClC(O)O-*i*-Bu with a tertiary amine (e.g. triethylamine, DIPEA, *N*-methylmorpholine) in the presence or absence of a pyridine derivative (e.g. pyridine, 4-(dimethylamino)pyridine, 4-pyrrolidinopyridine); or standard methods to prepare the activated ester can be applied, such as the use of 1-

hydroxybenazotriazole, 1-hydroxy-7-azabenzotriazole or pentafluorophenol in the presence of a coupling reagent (e.g. DCC, EDCI) or BOP.

In step (2b), standard methods to prepare the *N*-acyloxazolidinones (m = 0) can be employed. Illustrative examples of this chemistry are outlined in *Aldrichchimica Acta* 1997, Vol. 30, pp. 3 – 12 and the references therein; or standard methods to prepare the *N*-acyloxazinanone (m = 1) can be employed. An illustrative example of this chemistry is outlined in *Organic and Biomolecular Chemistry* 2006, Vol. 4, No. 14, pp. 2753 – 2768.
In step (2c), standard methods for alkylation can be employed. An illustrative example is outlined in *Chemical Reviews* 1996, 96(2), 835 – 876 and the references therein.
In step (2d), standard methods for cleavage of *N*-acyloxazolidinone or *N*-acyloxazinanone can be employed. Illustrative examples of this chemistry are outlined in *Aldrichchimica Acta* 1997, Vo. 30, pp. 3 – 12 and the references therein.

The intermediate H or I can be prepared according to the following general procedures described in Schemes 3 and 4:



Scheme 3

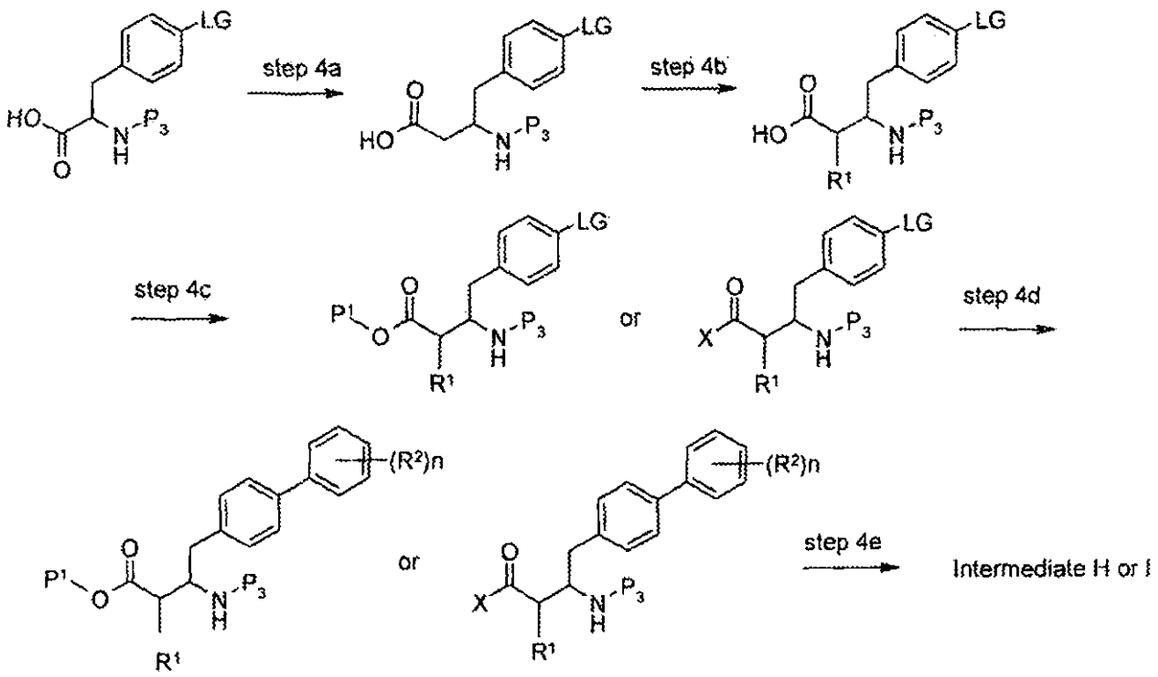
wherein R^1, R^2, X and n are as defined above and wherein P_3 is a protecting group selected from, but not limited to, *tert*-butyl, benzyl, triphenylphosphynyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, allyloxycarbonyl, acetyl or trifluoroacetyl.

In step (3a), standard methods for introduction of the amine part can be employed, such as using: either simultaneous treatment with or stepwise treatment via the corresponding acyl azide formation by using thionyl chloride (or $ClCO_2R^8$), NaN_3 (or $TMSN_3$) and R^9OH (wherein R^8 and R^9 are hydrogen, methyl, ethyl, tert-butyl, allyl, benzyl or 4-methoxybenzyl); or either simultaneous treatment with or stepwise treatment via the corresponding acyl azide formation with DPPA and R^9OH (wherein R^9 is defined as above); or standard methods for conversion to the corresponding carboxamide followed by treatment with NH_3 equivalent and either simultaneous treatment with or stepwise treatment with LTA or hypervalent iodine reagents (e.g. PIDA, PIFA, PhI(OH)OTs, PhIO) and R^9OH (wherein R^9 is defined as above); or standard methods for conversion to the corresponding carboxamide and either simultaneous treatment with or stepwise treatment with

Br_2 and MOH (wherein M is defined herein e.g. Na, K, Ba or Ca); or standard methods for conversion to the corresponding carboxamide and treatment with MOZ or $NaBrO_2$ (wherein Z is defined herein e.g. Cl or Br); or standard methods for conversion to the corresponding carboxamide and treatment with $Pb(OAc)_4$ and R^9OH (wherein R^9 is defined as above); or standard methods for conversion to the corresponding hydroxamic acid followed by treatment with H_2NOH or H_2NOTMS and treatment with Ac_2O, Boc_2O, $R^{10}COCl$, $R^{10}SO_2Cl$, $R^{10}PO_2Cl$ (wherein R^{10} is defined herein e.g. Me, Et, tBu or phenyl), thionyl chloride, EDCI, DCC, or 1-chloro-2,4-dinitrobenzene in the presence or absence of a base (e.g. pyridine, Na_2CO_3aq, triethylamine, DIPEA) and treatment with R^9OH in the presence of a base (e.g. DBU, ZOH, DIPEA) (wherein R^9 and Z are defined as above).

In step (3b), standard methods for removing P_3 protecting groups can be applied, such as base hydrolysis using NaOH, KOH, or LiOH, acid hydrolysis using TFA or HCl, or hydrogenation using palladium-on-carbon under hydrogen.

Scheme 4 describes an alternative synthesis of Intermediate H or I:



Scheme 4

wherein LG is a leaving group selected from, but not limited to, Cl, Br, I, OMs, OTs or OTf.

In step (4a), standard methods for Arndt-Eistert homologation can be employed. An illustrative example of this chemistry is outlined in "Enantioselective synthesis of β-amino acids, 2nd Edition", John Wiley and Sons, Inc., NJ (2005), either directly or analogously.
In step (4b), standard methods for alkylation can be employed, such as using R^1LG in the presence of a base such as LDA, NHMDS, LHMDS or KHMDS.
In step (4c), standard methods to protect the carboxylic acid can be employed, such as using $TMSCHN_2$ (for methyl ester), P^1LG/base (e.g. K_2CO_3, $NaHCO_3$, Cs_2CO_3 or K_3PO_4), thionyl chloride (or oxalyl chloride)/R^9OH, DCC(or EDCI)/DMAP/R^9OH, BOP/R^9OK (or R^9ONa), $(R^9O)_2CHNMe_2$, CDI/DBU/ R^9OH wherein R^9 has the same meaning as defined above, or isobutylene/H_2SO_4 (for tert-butyl ester).
In step (4d), standard methods for Suzuki coupling reaction can be applied, such as using a palladium (or nickel) species [e.g. $Pd(PPh_3)_4$, $PdCl_2(dppf)$, $Pd(OAc)_2$/a phosphine (e.g. PPh_3, dppf, PCy_3, $P(tBu)_3$, XPhos), Pd/C, $Pd_2(dba)_3$/ a phosphine (e.g. PPh_3, dppf, PCy_3, $P(tBu)_3$, XPhos), $Ni(COD)_2$/a phosphine (or dppe, dppb, PCy_3), $Ni(dppf)Cl_2$], a base (e.g. KF, CsF, K_3PO_4, Na_2CO_3, K_2CO_3, Cs_2CO_3, NaOH, KOH, NaO-*t*-Bu, KO-*t*-Bu), and $(R^2)n$-$PhB(OH)_2$ [or $(R^2)n$-$PhBF_3K$].
In step (4e), standard methods for removing P_3 protecting groups can be applied, such as base hydrolysis using NaOH, KOH, or LiOH, acid hydrolysis using TFA or HCl, or hydrogenation using palladium-on-carbon under hydrogen.
Alternatively, the intermediate H or I may be prepared be following the synthetic routes outlined in *Tetrahedron Letters*, 2008, Vol. 49, No. 33, pp. 4977-4980 either directly or analogously and converting the obtained boronic acid into a substituted biphenyl by methods outlined in *Organic Letters*, 2002, Vol. 4, No. 22, pp. 3803 – 3805.

Alternatively, the intermediate H or I may be prepared be following the synthetic routes outlined in *Tetrahedron: Asymmetry*, 2006, Vol. 17, No. 2, pp. 205-209 either directly or analogously.

Alternatively, the intermediate H or I may be prepared by methods of Mannich reaction. Illustrative examples of this chemistry are outlined in "Enantioselective synthesis of β-amino acids, 2nd Edition", John Wiley and Sons, Inc., NJ (2005), either directly or analogously.

Alternatively, the intermediate H or I may be prepared by enolate addition. Illustrative examples of this chemistry are outlined in "Enantioselective synthesis of β-amino acids, 2nd Edition", John Wiley and Sons, Inc., NJ (2005), either directly or analogously.

Alternatively, the intermediate H or I may be prepared by methods of aza-Michael reaction. Illustrative examples of this chemistry are outlined in "Enantioselective synthesis of β-amino acids, 2nd Edition", John Wiley and Sons, Inc., NJ (2005), either directly or analogously.

Alternatively, the intermediate H or I may be prepared following the synthetic route outlined in Synlett, 2006, No. 4, pp. 539-542, either directly or analogously.

The synthesis of intermediates J, K and L is also described in US patent application of applicant docket number PAT053600-US-USP3 which was filed on April 16, 2010, which application is incorporated herein by reference.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known *per se*.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration, and rectal administration, etc. In addition, the pharmaceutical compositions of the present invention can be made up in a solid form including capsules, tablets, pills, granules, powders or suppositories, or in a liquid form including solutions, suspensions or emulsions. The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifers and buffers etc.

Typically, the pharmaceutical compositions are tablets and gelatin capsules comprising the active ingredient together with

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

e) absorbents, colorants, flavors and sweeteners.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable compositions for oral administration include an effective amount of a compound of the invention in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Certain injectable compositions are aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating

methods, respectively, and contain about 0.1-75%, or contain about 1-50%, of the active ingredient.

Suitable compositions for transdermal application include an effective amount of a compound of the invention with carrier. Carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable compositions for topical application, *e.g.*, to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, *e.g.*, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

As used herein a topical application may also pertain to an inhalation or to an intranasal application. They are conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomizer or nebuliser, with or without the use of a suitable propellant.

The present invention further provides anhydrous pharmaceutical compositions and dosage forms comprising the compounds of the present invention as active ingredients, since water may facilitate the degradation of certain compounds.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e. g.*, vials), blister packs, and strip packs.

The invention further provides pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the compound of the present

invention as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

The compounds according to anyone of formulae I' and I to VIIC in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, e.g. neutral endopeptidase EC 3.4. 24.11 modulating properties, e.g. as indicated in in vitro and in vivo tests as provided in the next sections and are therefore indicated for therapy.

Compounds of the invention, or a pharmaceutically acceptable salt thereof, may be useful in the treatment of an indication selected from: cardiovascular disorders, such hypertension, pulmonary hypertension, isolated systolic hypertension, resistant hypertension, peripheral vascular disease, heart failure, congestive heart failure, left ventricular hypertrophy, angina, renal insufficiency, renal failure (including edema and salt retension), diabetic nephropathy, non-diabetic nephropathy, cyclical oedema, Menières disease, hyperaldosteroneism (primary and secondary) and hypercalciuria, ascites, glaucoma, menstrual disorders, preterm labour, pre-eclampsia, endometriosis, and reproductive disorders (especially male and female infertility, polycystic ovarian syndrome, implantation failure), asthma, obstructive sleep apnea, inflammation, leukemia, pain, epilepsy, affective disorders such as depression and psychotic condition such as dementia and geriatric confusion, obesity and gastrointestinal disorders (especially diarrhea and irritable bowel syndrome), wound healing (especially diabetic and venous ulcers and pressure sores), septic shock, the modulation of gastric acid secretion, the treatment of hyperreninaemia, cystic fibrosis, restenosis, type-2 diabetes, diabetic complications and atherosclerosis, male and female sexual dysfunction.

Thus, as a further embodiment, the present invention provides the use of a compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof. In a further embodiment, the therapy is selected from a disease which is ameliorated by inhibition of neutral endopeptidase EC 3.4. 24.11. In another embodiment, the disease is selected from the afore-mentioned list, suitably hypertension, pulmonary hypertension, isolated systolic hypertension, resistant hypertension, peripheral vascular disease, heart failure, congestive heart failure, left ventricular hypertrophy, angina, renal insufficiency, renal failure (including edema and salt retension), diabetic nephropathy, non-diabetic nephropathy, type-2 diabetis, and diabetic complications and most suitably cardiovascular disorders, such as hypertension, renal insufficiency including edema and congestive heart failure.

In another embodiment, the invention provides a method of treating a disease which is ameliorated by the inhibition of neutral endopeptidase EC 3.4. 24.11 comprising administration of a therapeutically acceptable amount of a compound according to anyone of formulae I', I, IA, II, IIA, III, IIIA, IV, IVA, V, VA, VI, VIA and VII to VIIC, or a pharmaceutically acceptable salt thereof. In a further embodiment, the disease is selected from the afore-mentioned list, suitably hypertension, pulmonary hypertension, isolated systolic hypertension, resistant hypertension, peripheral vascular disease, heart failure, congestive heart failure, left ventricular hypertrophy, angina, renal insufficiency, renal failure (including edema and salt retension), diabetic nephropathy, non-diabetic nephropathy, type-2 diabetes, and diabetic complications and most suitably cardiovascular disorders, such as hypertension, renal insufficiency including edema and congestive heart failure.

The pharmaceutical composition or combination of the present invention can be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg, or about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, *e.g.*, mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention can be applied *in vitro* in the form of solutions, *e.g.*, preferably aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, *e.g.*, as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg, or between about 1-100 mg/kg.

The activity of a compound according to the present invention can be assessed by the following *in vitro & in vivo* methods and/or by the following *in vitro & in vivo* methods well-described in the art. See A fluorescence lifetime-based assay for protease inhibitor profiling on human kallikrein 7 Doering K, Meder G, Hinnenberger M, Woelcke J, Mayr LM, Hassiepen U Biomol Screen. 2009 Jan; 14(1):1-9.

In particular, the *in vitro* inhibition of recombinant human neutral endopeptidase (NEP, EC 3.4.24.11) can be determined as follows:

Recombinant human neutral endopeptidase (expressed in insect cells and purified using standard methods, final concentration 7 pM) is pre-incubated with test compounds at various concentrations for 1 hour at room temperature in 10 mM sodium phosphate buffer at pH 7.4, containing 150 mM NaCl and 0.05 % (w/v) CHAPS. The enzymatic reaction is started by the addition of a synthetic peptide substrate Cys(PT14)-Arg-Arg-Leu-Trp-OH to a final concentration of 0.7 µM. Substrate hydrolysis leads to an increase fluorescence lifetime (FLT) of PT14 measured by the means of a FLT reader as described by Doering et al. (2009). The effect of the compound on the enzymatic activity was determined after 1 hour (t ≈ 60 min) incubation at room temperature. The IC50 values, corresponding to the inhibitor concentration showing 50% reduction of the FLT values measured in absence of inhibitor, are calculated from the plot of percentage of inhibition *vs.* inhibitor concentration using non-linear regression analysis software.

Using the test assay (as described above) compounds of the invention exhibited inhibitory efficacy in accordance to Table 1, provided *infra*.

Table 1 Inhibitory Activity of Compounds

Example #	Human NEP IC_{50} (nM)
Example 3-25	18
Example 3-26	15
Example 3-27	15
Example 5-1	38
Example 5-4	7
Example 5-7	4
Example 5-11	3
Example 5-12	67
Example 5-36	42
Example 5-37	2.3
Example 5-39	0.7
Example 5-46	0.5
Example 5-47	2.7
Example 5-55	0.7
Example 6-1	75
Example 9-1	56
Example 11-1	1.1
Example 11-11	0.5
Example 11-14	0.07
Example 12-1	0.2
Example 14-1	0.8
Example 15-1	1.2

The compound of the present invention may be administered either simultaneously with, or before or after, at least one other therapeutic agent. The compound of the present invention may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition.

In one embodiment, the invention provides a product comprising a compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, and at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a disease or condition associated with neutral endopeptidase EC 3.4. 24.11 activity. Products provided as a combined preparation include a composition comprising the compound of formulae I' and I to VIIC and the other therapeutic agent(s) together in the same pharmaceutical composition, or the compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, and the other therapeutic agent(s) in separate form, *e.g.* in the form of a kit.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, and another therapeutic agent(s). Optionally, the pharmaceutical composition may comprise a pharmaceutically acceptable excipient, as described above.

In one embodiment, the invention provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof. In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

The kit of the invention may be used for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit of the invention typically comprises directions for administration.

In the combination therapies of the invention, the compound of the invention, or a pharmaceutically acceptable salt thereof and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the invention, or a pharmaceutically acceptable salt thereof, and the other therapeutic may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (*e.g.* in the case of a kit comprising the compound of the

invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, *e.g.* during sequential administration of the compound of the invention and the other therapeutic agent.

Accordingly, the invention provides the use of a compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition associated with neutral endopeptidase EC 3.4. 24.11. activity, wherein the medicament is prepared for administration with another therapeutic agent. The invention also provides the use of another therapeutic agent in the manufacture of medicament for treating a disease or condition associated with neutral endopeptidase EC 3.4. 24.11. activity, wherein the medicament is prepared for administration with a compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof.

The invention also provides a compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, for use in a method of treating a disease or condition associated with neutral endopeptidase EC 3.4. 24.11 activity, wherein the compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, is prepared for administration with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a disease or condition associated with neutral endopeptidase EC 3.4. 24.11 activity, wherein the other therapeutic agent is prepared for administration with a compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof. The invention also provides a compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, for use in a method of treating a disease or condition associated with neutral endopeptidase EC 3.4. 24.11 activity, wherein the compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, is administered with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a disease or condition associated with neutral endopeptidase EC 3.4. 24.11 activity, wherein the other therapeutic agent is administered with a compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof.

The invention also provides the use of a compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition associated with neutral endopeptidase EC

3.4. 24.11 activity, wherein the patient has previously (*e.g.* within 24 hours) been treated with another therapeutic agent. The invention also provides the use of another therapeutic agent in the manufacture of a medicament for treating a disease or condition associated with neutral endopeptidase EC 3.4. 24.11 activity, wherein the patient has previously (*e.g.* within 24 hours) been treated with a compound according to anyone of formulae I' and I to VIIC, or a pharmaceutically acceptable salt thereof.

In one embodiment, the other therapeutic agent is selected from: HMG-Co-A reductase inhibitor, an anigiotensin receptor blocker (ARBs, angiotensin II receptor antagonist), angiotensin converting enzyme (ACE) inhibitor, a calcium channel blocker (CCB), an endothelin antagonist, a renin inhibitor, a diuretic, an ApoA-I mimic, an anti-diabetic agent, an obesity-reducing agent, an aldosterone receptor blocker, an endothelin receptor blocker, an aldosterone synthase inhibitors (ASI), a CETP inhibitor or a phophodiesterase type 5 (PDE5) inhibitor.

The term "in combination with" a second agent or treatment includes co-administration of the compound of the invention (*e.g.*, a compound of Formulae I' or I-VIIC or a compound otherwise described herein) with the second agent or treatment, administration of the compound of the invention first, followed by the second agent or treatment and administration of the second agent or treatment first, followed by the compound of the invention.

The term "second agent" includes any agent which is known in the art to treat, prevent, or reduce the symptoms of a disease or disorder described herein, *e.g* .a disorder or disease responsive to the inhibition of neutral endopeptidase, such as for example, hypertension, pulmonary hypertension, isolated systolic hypertension, resistant hypertension, peripheral vascular disease, heart failure, congestive heart failure, left ventricular hypertrophy, angina, renal insufficiency (diabetic or non-diabetic), renal failure (including edema and salt retension), diabetic nephropathy, non-diabetic nephropathy, nephroic syndrome, glomerulonephritis, scleroderma, glomerular sclerosis, proteinurea of primary renal disease, renal vascular hypertention, diabetic retinopathy and end-stage renal disease (ESRD), endothelial dysfunction, diastolic dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation (AF), cardiac fibrosis,atrial flutter, detrimental vascular remodeling, plaque stabilization, myocardial infarction (MI), renal fibrosis, polycystic kidney disease (PKD), pulmonary arterial hypertension, renal failure (including edema and salt retension), cyclical oedema, Menières disease, hyperaldosteroneism (primary and secondary) and hypercalciuria, ascites,

glaucoma, menstrual disorders, preterm labour, pre-eclampsia, endometriosis, and reproductive disorders (especially male and female infertility, polycystic ovarian syndrome, implantation failure), asthma, obstructive sleep apnea, inflammation, leukemia, pain, epilepsy, affective disorders such as depression and psychotic condition such as dementia and geriatric confusion, obesity and gastrointestinal disorders (especially diarrhea and irritable bowel syndrome), wound healing (especially diabetic and venous ulcers and pressure sores), septic shock, gastric acid secretion dysfunction, hyperreninaemia, cystic fibrosis, restenosis, type-2 diabetes, metabolic syndrome, diabetic complications and atherosclerosis, male and female sexual dysfunction.

Examples of second agents include HMG-Co-A reductase inhibitors, angiotensin II receptor antagonists, angiotensin converting enzyme (ACE) Inhibitors, calcium channel blockers (CCB), endothelin antagonists, renin inhibitors, diuretics, ApoA-I mimics, anti-diabetic agents, obesity-reducing agents, aldosterone receptor blockers, endothelin receptor blockers, aldosterone synthase inhibitors (ASI) and CETP inhibitors.

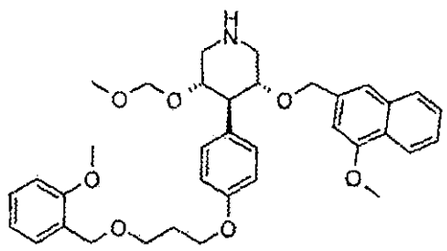
The term "HMG-Co-A reductase inhibitor" (also called beta-hydroxy-beta-methylglutaryl-co-enzyme-A reductase inhibitors) includes active agents that may be used to lower the lipid levels including cholesterol in blood. Examples include atorvastatin, cerivastatin, compactin, dalvastatin, dihydrocompactin, fluindostatin, fluvastatin, lovastatin, pitavastatin, mevastatin, pravastatin, rivastatin, simvastatin, and velostatin, or, pharmaceutically acceptable salts thereof.

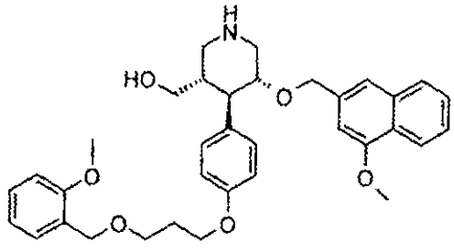
The term "ACE-inhibitor" (also called angiotensin converting enzyme inhibitors) includes molecules that interrupt the enzymatic degradation of angiotensin I to angiotensin II. Such compounds may be used for the regulation of blood pressure and for the treatment of congestive heart failure. Examples include alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, and trandolapril, or, pharmaceutically acceptables salt thereof.

The term "endothelin antagonist" includes bosentan (cf. EP 526708 A), tezosentan (cf. WO 96/19459), or, pharmaceutically acceptable salts thereof.

The term "renin inhibitor" includes ditekiren (chemical name: [1*S*-[1*R**,2*R**,4*R**(1*R**,2*R**)]]-1-[(1,1-dimethylethoxy)carbonyl]-L-prolyl-L-phenylalanyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmrthyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-*N*-alfa-methyl-L-histidinamide); terlakiren (chemical name: [*R*-(*R**,*S**)]-N-(4-morpholinylcarbonyl)-L-phenylalanyl-N-[1-

(cyclohexylmethyl)-2-hydroxy-3-(1-methylethoxy)-3-oxopropyl]-S-methyl-L-cysteineamide); Aliskiren (chemical name: (2*S*,4*S*,5*S*,7*S*)-5-amino-*N*-(2-carbamoyl-2,2-dimethylethyl)-4-hydroxy-7-{[4-methoxy-3-(3-methoxypropoxy) phenyl]methyl}-8-methyl-2-(propan-2-yl)nonanamide) and zankiren (chemical name: [1*S*-[1*R**[*R**(*R**)],2*S**,3*R**]]-*N*-[1-(cyclohexylmethyl)-2,3-dihydroxy-5-m ethylhexyl]-alfa-[[2-[[(4-methyl-1-piperazinyl)sulfonyl]methyl]-1-oxo-3-phenylpropyl]-amino]-4-thiazolepropanamide), or, hydrochloride salts thereof, or, SPP630, SPP635 and SPP800 as developed by Speedel, or RO 66-1132 and RO 66-1168 of Formula (A) and (B):



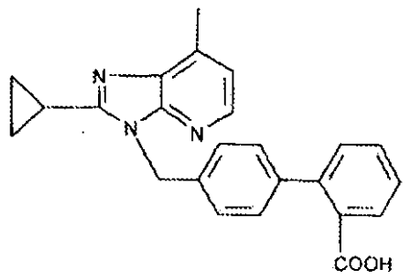
(A) and  (B), or,

pharmaceutically acceptable salts thereof.

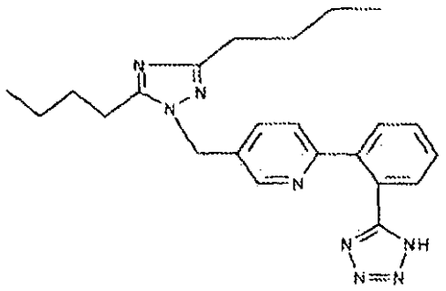
The term "aliskiren", if not defined specifically, is to be understood both as the free base and as a salt thereof, especially a pharmaceutically acceptable salt thereof, most preferably a hemi-fumarate salt thereof.

An angiotensin II receptor antagonist or a pharmaceutically acceptable salt thereof is understood to be an active ingredient which bind to the AT_1-receptor subtype of angiotensin II receptor but do not result in activation of the receptor. As a consequence of the inhibition of the AT_1 receptor, these antagonists can, for example, be employed as antihypertensives or for treating congestive heart failure.

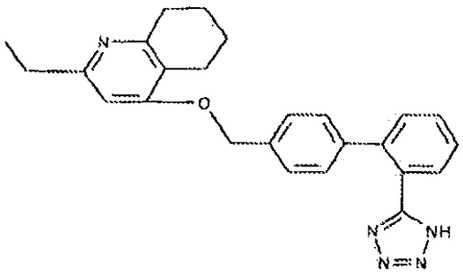
The class of AT_1 receptor antagonists comprises compounds having differing structural features, essentially preferred are the non-peptidic ones. For example, mention may be made of the compounds which are selected from the group consisting of valsartan, losartan, candesartan, eprosartan, irbesartan, saprisartan, tasosartan, telmisartan, the compound with the designation E-1477 of the following formula



the compound with the designation SC-52458 of the following formula



and the compound with the designation ZD-8731 of the following formula



or, in each case, a pharmaceutically acceptable salt thereof.

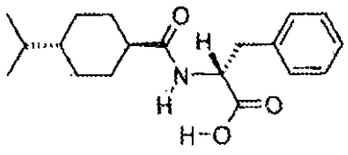
Preferred AT_1-receptor antagonist are those agents which have been marketed, most preferred is valsartan or a pharmaceutically acceptable salt thereof.

The term "calcium channel blocker (CCB)" includes dihydropyridines (DHPs) and non-DHPs (*e.g.*, diltiazem-type and verapamil-type CCBs). Examples include amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine, and is preferably a non-DHP representative selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibefradil, anipamil, tiapamil and verapamil, or, pharmaceutically acceptable salts thereof. CCBs may be used as anti-hypertensive, anti-angina pectoris, or anti-arrhythmic drugs.

The term "diuretic" includes thiazide derivatives (*e.g.*, chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidon).

The term "ApoA-I mimic" includes D4F peptides (*e.g.*, formula D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F)

The term "anti-diabetic agent" includes insulin secretion enhancers that promote the secretion of insulin from pancreatic β-cells. Examples include biguanide derivatives (*e.g.*, metformin), sulfonylureas (SU) (*e.g.*, tolbutamide, chlorpropamide, tolazamide, acetohexamide, 4-chloro-*N*-[(1-pyrolidinylamino)carbonyl]-benzensulfonamide (glycopyramide), glibenclamide (glyburide), gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibonuride, glipizide, gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, and tolylcyclamide), or pharmaceutically acceptable salts thereof. Further examples include phenylalanine derivatives (*e.g.*, nateglinide [*N*-(*trans*-4-isopropylcyclohexylcarbonyl)-*D*-phenylalanine] (cf. EP 196222 and EP 526171) of the formula



);

repaglinide [(*S*)-2-ethoxy-4-{2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl}benzoic acid] (cf. EP 589874, EP 147850 A2, in particular Example 11 on page 61, and EP 207331 A1); calcium (2*S*)-2-benzyl-3-(*cis*-hexahydro-2-isoindolinlycarbonyl)-propionate dihydrate (*e.g.*, mitiglinide (cf. EP 507534)); and glimepiride (cf. EP 31058). Further examples include DPP-IV inhibitors, GLP-1 and GLP-1 agonists.

DPP-IV is responsible for inactivating GLP-1. More particularly, DPP-IV generates a GLP-1 receptor antagonist and thereby shortens the physiological response to GLP-1. GLP-1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal.

The DPP-IV inhibitor can be peptidic or, preferably, non-peptidic. DPP-IV inhibitors are in each case generically and specifically disclosed *e.g.* in WO 98/19998, DE 196 16 486 A1, WO 00/34241 and WO 95/15309, in each case in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to these publications. Preferred are those compounds that are

specifically disclosed in Example 3 of WO 98/19998 and Example 1 of WO 00/34241, respectively.

GLP-1 is an insulinotropic protein which is described, *e.g.*, by W.E. Schmidt et al. in *Diabetologia*, 28, 1985, 704-707 and in US 5,705,483.

The term "GLP-1 agonists" includes variants and analogs of GLP-1(7-36)NH_2 which are disclosed in particular in US 5,120,712, US 5,118666, US 5,512,549, WO 91/11457 and by C. Orskov et al in J. Biol. Chem. 264 (1989) 12826. Further examples include GLP-1(7-37), in which compound the carboxy-terminal amide functionality of Arg^{36} is displaced with Gly at the 37th position of the GLP-1(7-36)NH_2 molecule and variants and analogs thereof including GLN^{9}-GLP-1(7-37), D-GLN^{9}-GLP-1(7-37), acetyl LYS^{9}-GLP-1(7-37), LYS^{18}-GLP-1(7-37) and, in particular, GLP-1(7-37)OH, VAL^{8}-GLP-1(7-37), GLY^{8}-GLP-1(7-37), THR^{8}-GLP-1(7-37), MET^{8}-GLP-1(7-37) and 4-imidazopropionyl-GLP-1. Special preference is also given to the GLP agonist analog exendin-4, described by Greig *et al.* in Diabetologia 1999, 42, 45-50.

Also included in the definition "anti-diabetic agent" are insulin sensitivity enhancers which restore impaired insulin receptor function to reduce insulin resistance and consequently enhance the insulin sensitivity. Examples include hypoglycemic thiazolidinedione derivatives (*e.g.*, glitazone, (*S*)-((3,4-dihydro-2-(phenyl-methyl)-2*H*-1-benzopyran-6-yl)methyl-thiazolidine-2,4-dione (englitazone), 5-{[4-(3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl)-phenyl]-methyl}-thiazolidine-2,4-dione (darglitazone), 5-{[4-(1-methyl-cyclohexyl)methoxy)-phenyl]methyl}-thiazolidine-2,4-dione (ciglitazone), 5-{[4-(2-(1-indolyl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione (DRF2189), 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy)]benzyl}-thiazolidine-2,4-dione (BM-13.1246), 5-(2-naphthylsulfonyl)-thiazolidine-2,4-dione (AY-31637), bis{4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenyl}methane (YM268), 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-thiazolidine-2,4-dione (AD-5075), 5-[4-(1-phenyl-1-cyclopropanecarbonylamino)-benzyl]-thiazolidine-2,4-dione (DN-108) 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione, 5-[3-(4-chloro-phenyl])-2-propynyl]-5-phenylsulfonyl)thiazolidine-2,4-dione, 5-[3-(4-chlorophenyl])-2-propynyl]-5-(4-fluorophenyl-sulfonyl)thiazolidine-2,4-dione, 5-{[4-(2-(methyl-2-pyridinyl-amino)-ethoxy)phenyl]methyl}-thiazolidine-2,4-dione (rosiglitazone), 5-{[4-(2-(5-ethyl-2-pyridyl)ethoxy)phenyl]-methyl}thiazolidine-2,4-dione (pioglitazone), 5-{[4-((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy)-phenyl]-methyl}-thiazolidine-2,4-dione (troglitazone), 5-[6-(2-fluoro-benzyloxy)naphthalen-2-ylmethyl]-thiazolidine-2,4-dione (MCC555), 5-{[2-(2-naphthyl)-benzoxazol-5-yl]-methyl}thiazolidine-2,4-

dione (T-174) and 5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-(4-trifluoromethyl-benzyl)benzamide (KRP297)).

Further anti-diabetic agents include, insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), antidiabetic non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT); compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-Bpase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK); pyruvate dehydrogenase kinase (PDHK) inhibitors; inhibitors of gastric emptying; insulin; inhibitors of GSK-3; retinoid X receptor (RXR) agonists; agonists of Beta-3 AR; agonists of uncoupling proteins (UCPs); non-glitazone type PPARγ agonists; dual PPARα/ PPARγ agonists; antidiabetic vanadium containing compounds; incretin hormones, like glucagon-like peptide-1 (GLP-1) and GLP-1 agonists; beta-cell imidazoline receptor antagonists; miglitol; α_2-adrenergic antagonists; and pharmaceutically acceptable salts thereof.

The term "obesity-reducing agent" includes lipase inhibitors (*e.g.*, orlistat) and appetite suppressants (*e.g.*, sibutramine and phentermine).

An aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof is understood to be an active ingredient that has the property to inhibit the production of aldosterone. Aldosterone synthase (CYP11B2) is a mitochondrial cytochrome P450 enzyme catalyzing the last step of aldosterone production in the adrenal cortex, i.e., the conversion of 11-deoxycorticosterone to aldosterone. The inhibition of the aldosterone production with so-called aldosterone synthase inhibitors is known to be a successful variant to treatment of hypokalemia, hypertension, congestive heart failure, atrial fibrillation or renal failure. Such aldosterone synthase inhibition activity is readily determined by those skilled in the art according to standard assays (*e.g.*, US 2007/0049616).

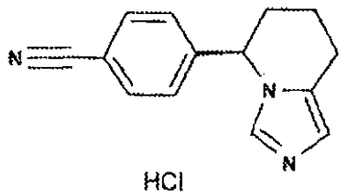
The class of aldosterone synthase inhibitors comprises both steroidal and non-steroidal aldosterone synthase inhibitors, the later being most preferred.

Preference is given to commercially available aldosterone synthase inhibitors or those aldosterone synthase inhibitors that have been approved by the health authorities.

The class of aldosterone synthase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting of the non-steroidal aromatase inhibitors anastrozole,

fadrozole (including the (+)-enantiomer thereof), as well as the steroidal aromatase inhibitor exemestane, or, in each case where applicable, a pharmaceutically acceptable salt thereof.

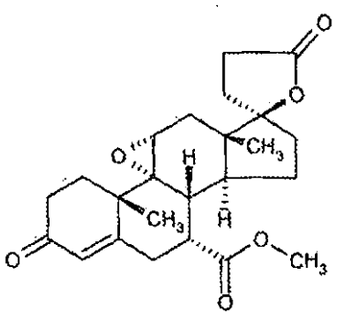
The most preferred non-steroidal aldosterone synthase inhibitor is the (+)-enantiomer of the hydrochloride of fadrozole (US patents 4617307 and 4889861) of formula



HCl

or, if appropriable, a pharmaceutically acceptable salt thereof.

A preferred steroidal aldosterone antagonist is eplerenone (cf. EP 122232 A) of the formula



or Spironolactone; or, in each case, if appropriable, a pharmaceutically acceptable salt thereof.

Aldosterone synthase inhibitors useful in said combination are compounds and analogs generically and specifically disclosed e.g. in US2007/0049616, in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to this publication. Preferred aldosterone synthase inhibitors suitable for use in the present invention include, without limitation 4-(6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-5-yl)-3-methylbenzonitrile; 5-(2-chloro-4-cyanophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole-5-carboxylic acid (4-methoxybenzyl)methylamide; 4'-fluoro-6-(6,7,8,9-tetrahydro-5*H*-imidazo[1,5-*a*]azepin-5-yl)biphenyl-3-carbonitrile; 5-(4-Cyano-2-methoxyphenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylic acid butyl ester; 4-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-2-methoxybenzonitrile; 5-(2-Chloro-4-cyanophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole-5-carboxylic acid 4-fluorobenzyl ester; 5-(4-Cyano-2-trifluoromethoxyphenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylic acid methyl

ester; 5-(4-Cyano-2-methoxyphenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole-5-carboxylic acid 2-isopropoxyethyl ester; 4-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-5-yl)-2-methylbenzonitrile; 4-(6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-5-yl)-3-fluorobenzonitrile ; 4-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-5-yl)-2-methoxybenzonitrile; 3-Fluoro-4-(7-methylene-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-5-yl)benzonitrile; *cis*-3-Fluoro-4-[7-(4-fluoro-benzyl)-5,6,7,8-tetrahydro-imidazo[1,5-a]pyridin-5-yl]benzonitrile; 4'-Fluoro-6-(9-methyl-6,7,8,9-tetrahydro-5*H*-imidazo[1,5-*a*]azepin-5-yl)biphenyl-3-carbonitrile; 4'-Fluoro-6-(9-methyl-6,7,8,9-tetrahydro-5*H*-imidazo[1,5-*a*]azepin-5-yl)biphenyl-3-carbonitrile or in each case, the (R) or (S) enantiomer thereof; or if appropriable, a pharmaceutically acceptable salt thereof.

The term aldosterone synthase inhibitors also include compounds and analogs disclosed in WO2008/076860, WO2008/076336, WO2008/076862, WO2008/027284, WO2004/046145, WO2004/014914, WO2001/076574.

Furthermore Aldosterone synthase inhibitors also include compounds and analogs disclosed in U.S. patent applications US2007/0225232, US2007/0208035, US2008/0318978, US2008/0076794, US2009/0012068, US20090048241 and in PCT applications WO2006/005726, WO2006/128853, WO2006128851, WO2006/128852, WO2007065942, WO2007/116099, WO2007/116908, WO2008/119744 and in European patent application EP 1886695. Preferred aldosterone synthase inhibitors suitable for use in the present invention include, without limitation 8-(4-Fluorophenyl)-5,6-dihydro-8H-imidazo[5,1-c1[1 ,41oxazine; 4-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)-2-fluorobenzonitrile; 4-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)-2,6-difluorobenzonitrile; 4-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)-2-methoxybenzonitrile; 3-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)benzonitrile; 4-(5,6-Dihvdro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)phthalonitrile; 4-(8-(4-Cyanophenyl)-5,6-dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)benzonitrile; 4-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)benzonitrile; 4-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)naphthalene-1-carbonitrile; 8-[4-(1 H-Tetrazol-5-yl)phenyl1-5,6-dihvdro-8H-imidazo[5,1-c][1 ,4]oxazine as developed by Speedel or in each case, the (R) or (S) enantiomer thereof; or if appropriable, a pharmaceutically acceptable salt thereof.

The term "endothelin receptor blocker" includes bosentan.

The term "CETP inhibitor" refers to a compound that inhibits the cholesteryl ester transfer protein (CETP) mediated transport of various cholesteryl esters and triglycerides from HDL to LDL and VLDL. Such CETP inhibition activity is readily determined by those skilled in the art according to standard assays (*e.g.*, U.S. Pat. No. 6,140,343). Examples include compounds disclosed in U.S. Pat. No. 6,140,343 and U. S. Pat. No. 6,197,786 (*e.g.*,

[2R,4S]4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl- amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (torcetrapib); compounds disclosed in U.S. Pat. No. 6,723,752 (*e.g.*, (2R)-3-{[3-(4-Chloro-3-ethyl-phenoxy)-phenyl]-[[3-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methyl]-amino}-1,1,1-trifluoro-2-propanol); compounds disclosed in U.S. patent application Ser. No. 10/807,838; polypeptide derivatives disclosed in U.S. Pat. No. 5,512,548; rosenonolactone derivatives and phosphate-containing analogs of cholesteryl ester disclosed in *J. Antibiot.*, 49(8): 815- 816 (1996), and *Bioorg. Med. Chem. Lett.*; 6:1951-1954 (1996), respectively. Furthermore, the CETP inhibitors also include those disclosed in WO2000/017165, WO2005/095409 and WO2005/097806.

A prefered PDE5 inhibitor is Sildenafil.

Second agent of particular interest include Endothelin antagonists, renin inhibitors, angiotensin II receptor antagonists, calcium channel blockers, diuretics, antidiabetic agents such as DPPIV inhibitors, and aldosterone synthase inhibitors.

EXEMPLIFICATION OF THE INVENTION:

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, NMR. Abbreviations used are those conventional in the art. The compounds in the example 5-1 to 15-3 have been found to have IC_{50} values in the range of about 0.01 nM to about 10,000 nM for NEP.

The conditions for measuring the retention times are as follows:

HPLC condition A:

Column: INERTSIL C8-3, 3µm x 33mm x 3.0mm at 40 °C

Flow rate: 2 ml / min
Mobile phase: A) 5 mM aqueous HCOONH4, B) MeOH / CH3CN (1 / 1, v / v)
Gradient: linear gradient from 5% A to 95% B in 2 min
Detection: DAD-UV at 200-400 nm

HPLC condition B:
Column: INERTSIL C8-3, 3µm x 33mm x 3.0mm at 40 °C
Flow rate: 2 ml / min
Mobile phase: A) 5 mM aqueous HCOONH4, B) MeOH / CH3CN (1 / 1, v / v)
Gradient: linear gradient from 40% A to 95% B in 2 min
Detection: DAD-UV at 200-400 nm

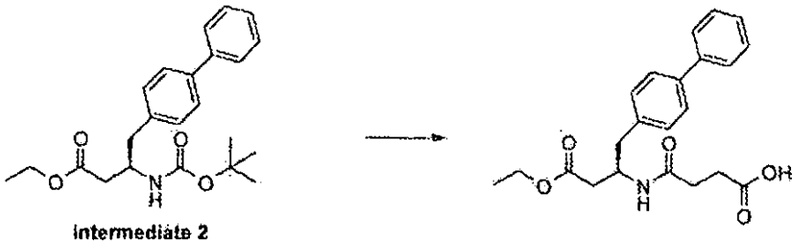
HPLC condition C:
Column: INERTSIL C8-3, 3µm x 33mm x 3.0mm at 40 °C
Flow rate: 2 ml / min
Mobile phase: A) (5 mM $NH_4^+HCOO^-$)/water, B) MeOH / CH_3CN (1 / 1, v / v)
Gradient: linear gradient from 5 to 95% B in 2 min
Detection: DAD-UV at 200-400 nm

HPLC condition D:
Column: INERTSIL C8-3, 3µm x 33mm x 3.0mm at 40 °C
Flow rate: 2 ml / min
Mobile phase: A) 0.1% aqueous Formic acid, B) MeOH / CH_3CN (1 / 1, v / v)
Gradient: linear gradient from 5% B to 95% B in 2 min
Detection: DAD-UV at 200-400 nm

HPLC condition E:
Column: Inertsil C8-3, 3µm x 33mm x 3.0mm at 40 °C
Flow rate: 2 ml / min
Mobile phase: A) methanol / acetonitrile (1 / 1, v / v), B) 5 mM aquesous $HCOONH_4$
Gradient: linear gradient from 40% B to 95% A in 2 min
Detection: UV at 214 nm

The relative stereochemistry was determined using two dimensional NMR. Under the reaction condition, it would be unexpected that the stereocenter bearing the bisphenyl-methyl group racemize. Therefore, the absolute stereochemistry was determined based on the relative stereochemistry and the absolute stereochemistry of the stereocenter bearing the bisphenyl-methyl group.

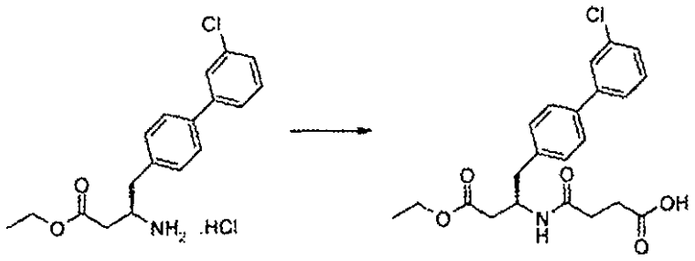
Example 1-1: Synthesis of (R)-4-(1-(biphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid



Intermediate 2

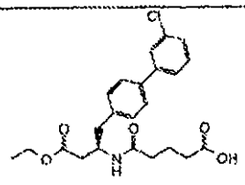
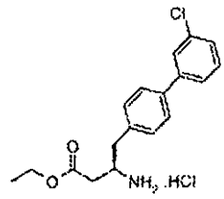
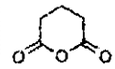
To (*R*)-ethyl-4-(biphenyl-4-yl)-3-(*tert*-butoxycarbonylamino)butanoate (230.1 mg, 0.600 mmol) is added a solution of HCl in 1,4-dioxane (3.00 mL, 12.00 mmol) at room temperature. After stirring for 1 hour, the reaction mixture is concentrated under reduced pressure to give (*R*)-3-amino-4-biphenyl-4-yl-butyric acid ethyl ester hydrochloride. A solution of (*R*)-3-amino-4-biphenyl-4-yl-butyric acid ethyl ester hydrochloride, succinic anhydride (72.1 mg, 0.720 mmol) and DIPEA (0.126 mL, 0.720 mmol) in dichloromethane (4 mL) is allowed to stir for 1 hour. The reaction is quenched with 10% aqueous citric acid and extracted with dichloromethane. The organic layer is separated and concentrated under reduced pressure. The obtained residue is purified by flash column chromatography on CN-modified silica gel (eluent: heptane/EtOAc = 100:0 to 0:100) and by RP-HPLC (SunFire C18, H_2O(0.1%TFA)/CH_3CN) to give (*R*)-4-(1-(biphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid (148.2 mg). HPLC retention time = 1.64 minutes (condition A); MS (m+1) = 384.1; 1H NMR (400 MHz, ACETONITRILE-*d*3) δ ppm 1.21 (t, *J*=7.07 Hz, 3 H) 2.31 - 2.39 (m, 2 H) 2.40 - 2.56 (m, 4 H) 2.77 - 2.92 (m, 2 H) 4.08 (q, *J*=7.24 Hz, 2 H) 4.33 - 4.48 (m, 1 H) 6.62 (d, *J*=8.34 Hz, 1 H) 7.30 (d, *J*=8.08 Hz, 2 H) 7.32 - 7.39 (m, 1 H) 7.41 - 7.49 (m, 2 H) 7.54 - 7.60 (m, 2H) 7.60 - 7.67 (m, 2 H) 10.02 (br. s., 1 H).

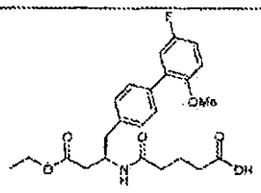
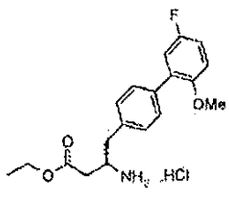
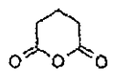
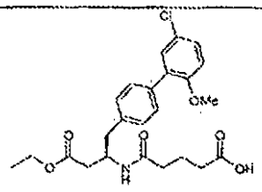
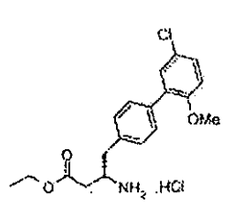
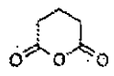
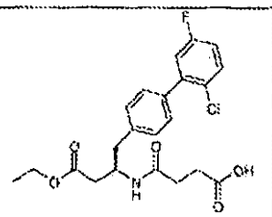
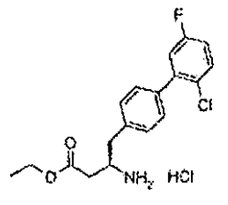
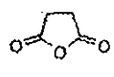
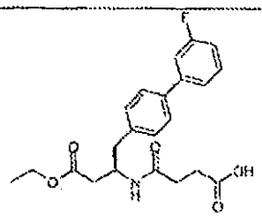
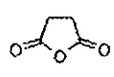
Example 1-2: Synthesis of (*R*)-4-(1-(3'-chlorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid

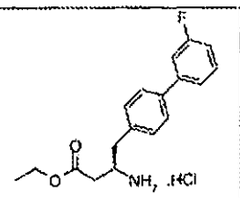
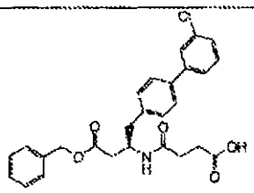
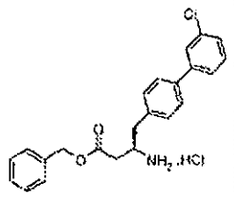
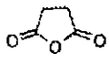
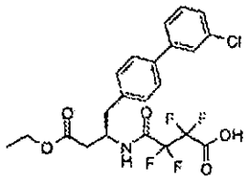
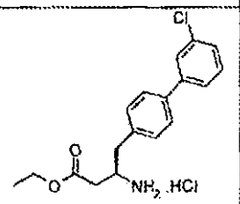
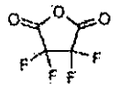
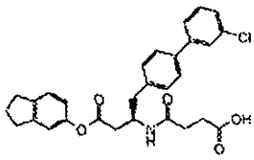
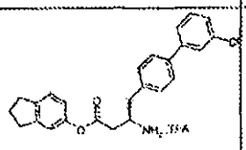
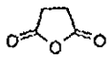


A solution of (*R*)-ethyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride (400 mg, 1.13 mmol), succinic anhydride (136 mg, 1.36 mmol) and DIPEA (0.237 mL, 1.36 mmol) in dichloromethane (5 mL) is allowed to stir for 2.5 hours. The reaction is quenched with 1 M aqueous HCl and extracted with dichloromethane. The organic layer is separated and concentrated under reduced pressure. The resulting residue is purified by preparative HPLC using a gradient of 20% MeCN/water (0.1% TFA) to 100% MeCN to give (*R*)-4-(1-(3'-chlorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid (255 mg). HPLC retention time = 1.15 minutes (condition B); MS (m+1) = 418.0; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J* = 7.08 Hz, 3 H) 2.46 - 2.58 (m, 4 H) 2.64 – 2.67 (m, 2 H) 2.87 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.99 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.6 Hz, 1 H) 4.12 – 4.24 (m, 2 H) 4.47 - 4.55 (m, 1 H) 6.50 (br d, *J* = 8.8 Hz, 1 H) 7.24 - 7.37 (m, 4 H) 7.43 - 7.46 (m, 1 H) 7.48 - 7.52 (m, 2H) 7.55 – 7.56 (m, 1 H).
Chiral HPLC retention time = 3.59 min. Column: Daicel CHIRALPAK AD-H (4.6x100mm); flow rate = 1 ml/min.; eluent: EtOH(containing 0.1% TFA)/heptane = 4/6.

Following compounds are prepared using similar procedure as described in example 1-2:

Example #	Product	Starting Material	Condition	HPLC-RT (condition)	MS (M+1)
Example 1-3	 (R)-5-(1-(3'-chlorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-5-oxopentanoic acid		 DIPEA, DCM, RT	1.57 min. (A)	432.1

Example 1-4	 (R)-5-(4-ethoxy-1-(5'-fluoro-2'-methoxybiphenyl-4-yl)-4-oxobutan-2-ylamino)-5-oxopentanoic acid		 DIPEA, DCM, RT	0.93 min. (B)	446.3
Example 1-5	 (R)-5-(1-(5'-chloro-2'-methoxybiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-5-oxopentanoic acid		 DIPEA, DCM, RT	1.14 min. (B)	462.5
Example 1-6	 (R)-4-(1-(2'-chloro-5'-fluorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid.		 DIPEA, DCM, RT	0.97 min. (B)	436.2
Example 1-7			 DIPEA, DCM, RT	1.23 min. (B)	402.0

	(R)-4-(4-ethoxy-1-(3'-fluorobiphenyl-4-yl)-4-oxobutan-2-ylamino)-4-oxobutanoic acid				
Example 1-8	 (R)-4-(4-(benzyloxy)-1-(3'-chlorobiphenyl-4-yl)-4-oxobutan-2-ylamino)-4-oxobutanoic acid		 DIPEA, DCM, RT	1.37 min. (B)	480.2
Example 1-9			 Pyridine, RT	1.32 min. (C)	490.2
Example 1-10			 DIPEA, DCM, RT	1.52 min. (B)	506.4

Example 1-3: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J* = 7.2 Hz, 3 H) 1.86 - 1.97 (m, 2 H) 2.25 - 2.28 (m, 2 H) 2.34 (t, *J* = 7.0 Hz, 2 H) 2.50 (A of ABX, J_{ab} = 16.2 Hz, *J*ax = 5.6 Hz, 1 H) 2.56 (B of ABX, J_{ab} = 16.2 Hz, J_{bx} = 5.1 Hz, 1 H) 2.88 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.98 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 7.1 Hz, 1 H) 4.12 - 4.23 (m, 2 H) 4.50 - 4.58 (m, 1 H) 6.32 (br d, *J* = 8.8 Hz, 1 H) 7.25 - 7.37 (m, 4 H) 7.43 - 7.46 (m, 1 H) 7.49 - 7.52 (m, 2 H) 7.55 - 7.56 (m, 1 H).

Example 1-4: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.29 (t, J = 7.1 Hz, 3 H) 1.86 - 1.97 (m, 2 H) 2.25 - 2.28 (m, 2 H) 2.34 (t, J = 7.0 Hz, 2 H) 2.54 (A of ABX, J_{ab} = 16.1 Hz, J_{ax} = 5.6 Hz, 1 H) 2.58 (B of ABX, J_{ab} = 16.1 Hz, J_{bx} = 5.2 Hz, 1 H) 2.88 (A of ABX, J_{ab} = 13.5 Hz, J_{ax} = 7.6 Hz, 1 H) 2.97 (B of ABX, J_{ab} = 13.5 Hz, J_{bx} = 7.0 Hz, 1 H) 3.78 (s, 3 H) 4.12 - 4.23 (m, 2 H) 4.50 - 4.59 (m, 1 H) 6.34 (br d, J = 8.6 Hz, 1 H) 6.88 - 6.91 (m, 1 H) 6.96 - 7.04 (m, 2 H) 7.23 (d, J = 8.3 Hz, 2 H) 7.44 - 7.47 (m, 2 H).

Example 1-5: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.29 (t, J = 7.1 Hz, 3 H) 1.86 - 1.97 (m, 2 H) 2.25 - 2.36 (m, 4 H) 2.49 - 2.61 (m, 2 H) 2.88 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.6 Hz, 1 H) 2.97 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.8 Hz, 1 H) 3.79 (s, 3 H) 4.12 - 4.23 (m, 2 H) 4.50 - 4.59 (m, 1 H) 6.34 - 6.36 (m, 1 H) 6.89 (d, J = 8.6 Hz, 1 H) 7.21 - 7.28 (m, 3 H) 7.43 (d, J = 8.1 Hz, 2 H).

Example 1-6: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.29 (t, J = 7.1 Hz, 3 H) 2.47 - 2.67 (m, 6 H) 2.89 (A of ABX, J_{ab} = 13.7 Hz, J_{ax} = 7.8 Hz, 1 H) 3.00 (B of ABX, J_{ab} = 13.7 Hz, J_{bx} = 6.7 Hz, 1 H) 4.12 - 4.24 (m, 2 H) 4.49 - 4.57 (m, 1 H) 6.51 (br d, J = 8.6 Hz, 1 H) 6.97 - 7.07 (m, 2 H) 7.24 - 7.26 (m, 2 H) 7.36 - 7.43 (m, 3 H).

Example 1-7: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.16 (t, J = 7.1 Hz, 3 H) 2.23 - 2.27 (m, 2 H) 2.34 - 2.38 (m, 2 H) 2.40 - 2.47 (m, 2 H) 2.77 (d, J = 6.6 Hz, 2 H) 3.99 - 4.06 (m, 2 H) 4.21 - 4.30 (m, 1 H) 7.14 - 7.19 (m, 1 H) 7.29 (d, J = 8.4 Hz, 2 H) 7.46 - 7.52 (m, 3 H) 7.63 (d, J = 8.4 Hz, 2 H) 7.91 (d, J = 8.3 Hz, 1 H) 12.04 (s, 1 H).

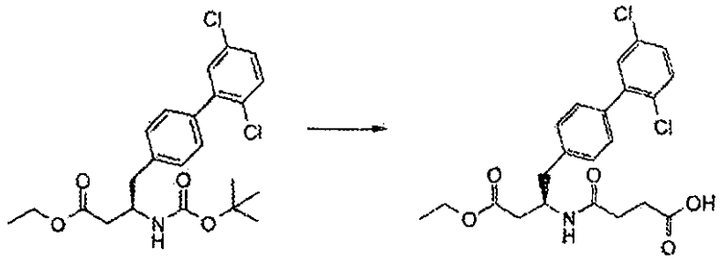
Example 1-8: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.41 - 2.45 (m, 2 H) 2.50 - 2.64 (m, 4 H) 2.81 - 2.87 (m, 1 H) 2.95 - 3.00 (m, 1 H) 4.49 – 4.56 (m, 1 H) 5.12 (A of AB, J = 12.1 Hz, 1 H) 5.18 (B of AB, J = 12.1 Hz, 1 H) 6.39 (d, J = 8.1 Hz, 1 H) 7.18 - 7.54 (m, 13 H).

Example 1-9: 1H NMR (400 MHz, DMSO-d6): 1H NMR (400 MHz, DMSO-d6): δ ppm 1.22-1.25 (t, J=7.07 Hz, 3H), 2.61-2.63 (m, 2H), 2.91 (d, J=7.07 Hz, 2H), 4.09 (q, J=7.07 Hz, 2H), 4.52-4.59 (m, 1H), 7.32-7.34 (m, 3H), 7.04 (t, J=7.83 Hz, 1H), 7.52-7.56 (m, 3H), 7.59 (t, J=2.02 Hz, 1H).

Example 1-10: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.03 - 2.13 (m, 2 H), 2.44 (t, J=6.3 Hz, 2 H), 2.64 (t, J=6.6 Hz, 2 H), 2.70 (dd, J=16.2, 5.6 Hz, 1 H), 2.78 (dd, J=16.2, 5.1

Hz, 1 H), 2.83 - 2.98 (m, 5 H), 3.04 (dd, J=13.9, 6.8 Hz, 1 H), 4.57 - 4.69 (m, 1 H), 6.51 (d, J=8.8 Hz, 1 H), 6.79 (dd, J=8.1, 2.3 Hz, 1 H), 6.90 (d, J=1.8 Hz, 1 H), 7.18 (d, J=8.1 Hz, 1 H), 7.26 - 7.31 (m, 3 H), 7.34 (t, J=7.7 Hz, 1 H), 7.43 (dt, J=7.3, 1.5 Hz, 1 H), 7.49 (d, J=8.1 Hz, 2 H), 7.54 (t, J=1.8 Hz, 1 H), 9.34 (br. s., 1 H).

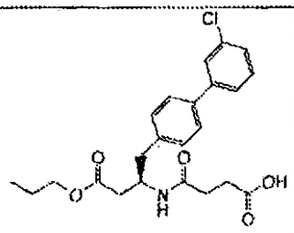
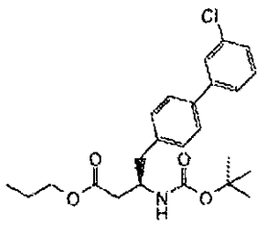
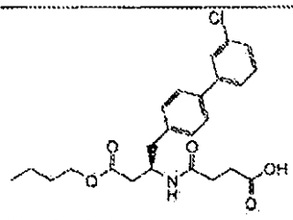
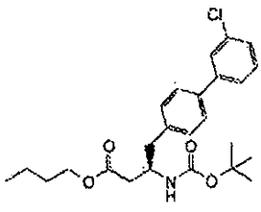
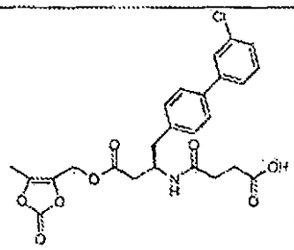
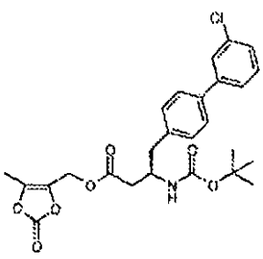
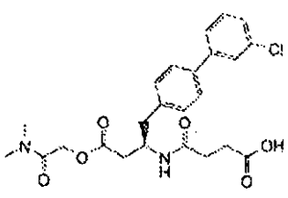
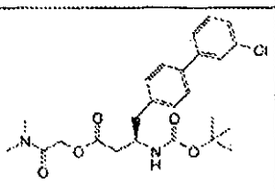
Example 1-11: Synthesis of (*R*)-4-(1-(2',5'-dichlorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid

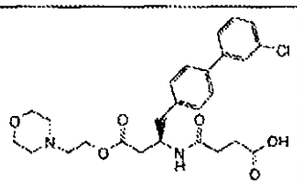
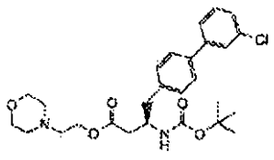


To (R)-ethyl 3-(tert-butoxycarbonylamino)-4-(2',5'-dichlorobiphenyl-4-yl)butanoate (1.09 g, 2.33 mmol) is added a solution of 4 M HCl in 1,4-dioxane (5.81 mL, 23.3 mmol) at room temperature. After stirring for 2 hours, the reaction mixture is concentrated under reduced pressure to give (*R*)-ethyl 3-amino-4-(2',5'-dichlorobiphenyl-4-yl)butanoate hydrochloride. Next, a solution of the product, succinic anhydride (280 mg, 2.80 mmol) and DIPEA (0.489 mL, 2.80 mmol) in dichloromethane (15 mL) is allowed to stir for 2 hours. The reaction is quenched with 1 M aqueous HCl and extracted with dichloromethane. The organic layer is separated and concentrated under reduced pressure. The resulting residue is purified by preparative HPLC using a gradient of 20% MeCN/water (0.1% TFA) to 100% MeCN to give (*R*)-4-(1-(2',5'-dichlorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid (553 mg) as a white solid; HPLC retention time = 1.02 minutes (condition B); MS (m+1) = 452.14; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J* = 7.2 Hz, 3 H) 2.47 - 2.67 (m, 6 H) 2.89 (A of ABX, J_{ab} = 13.7 Hz, J_{ax} = 7.8 Hz, 1 H) 3.00 (B of ABX, J_{ab} = 13.7 Hz, J_{bx} = 6.7 Hz, 1 H) 4.12 - 4.24 (m, 2 H) 4.49 - 4.57 (m, 1 H) 6.53 (br d, *J*= 8.8 Hz, 1 H) 7.23 - 7.26 (m, 3 H) 7.32 - 7.40 (m, 4 H).

Following compounds are prepared using similar procedure as described in example 1-11:

Example	Product	Srating Material	HPLC-RT (condition)	MS (M+1)

Example 1-12	 (R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-butyric acid propyl ester		1.24 min. (B)	432.3
Example 1-13	 (R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-butyric acid butyl ester		1.34 min. (B)	446.2
Example 1-14	 (R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-butyric acid 5-methyl-2-oxo-[1,3]dioxol-4-yl methyl ester		1.12 min. (B)	502.2
Example 1-15			0.89 min. (B)	475.3

	(R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-butyric acid dimethylcarbamoylmethyl ester			
Example 1-16	 (R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-butyric acid 2-morpholin-4-yl-ethyl ester		0.99 min. (B)	503.5

Example 1-12: 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.87 (t, J=7.5 Hz, 3 H), 1.49 - 1.61 (m, 2 H), 2.22 - 2.29 (m, 2 H), 2.32 - 2.39 (m, 2 H), 2.45 (dd, J=6.9, 3.4 Hz, 2 H), 2.78 (d, J=6.6 Hz, 2 H), 3.94 (t, J=6.6 Hz, 2 H), 4.21 - 4.33 (m, 1 H), 7.29 (d, J=8.3 Hz, 2 H), 7.37 - 7.42 (m, 1 H), 7.47 (t, J=7.8 Hz, 1 H), 7.58 - 7.65 (m, 3 H), 7.69 (t, J=1.9 Hz, 1 H), 7.92 (d, J=8.3 Hz, 1 H).

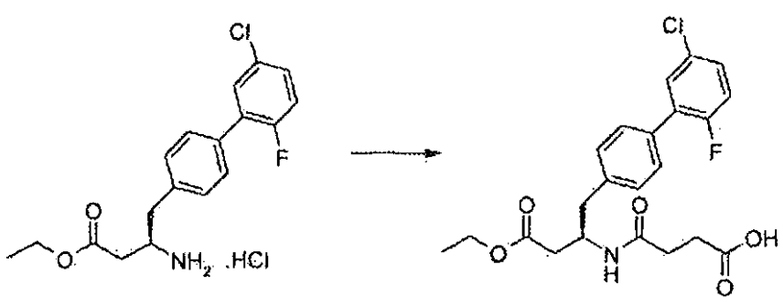
Example 1-13: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.94 (t, J=7.3 Hz, 3 H), 1.32 - 1.44 (m, 2 H), 1.56 - 1.67 (m, 2 H), 2.43 - 2.59 (m, 4 H), 2.65 (t, J=6.4 Hz, 2 H), 2.85 (dd, J=13.6, 8.1 Hz, 1 H), 2.99 (dd, J=13.6, 6.6 Hz, 1 H), 4.03 - 4.18 (m, 2 H), 4.43 - 4.56 (m, 1 H), 6.57 (d, J=8.6 Hz, 1 H), 7.25 (d, J=8.3 Hz, 2 H), 7.28 - 7.32 (m, 1 H), 7.35 (t, J=7.7 Hz, 1 H), 7.41 - 7.46 (m, 1 H), 7.48 (d, J=8.1 Hz, 2 H), 7.55 (t, J=1.8 Hz, 1 H).

Example 1-14: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.17 (s, 3 H), 2.44 (t, J=6.2 Hz, 2 H), 2.48 - 2.57 (m, 1 H), 2.57 - 2.73 (m, 3 H), 2.87 (dd, J=13.6, 7.6 Hz, 1 H), 2.98 (dd, J=13.9, 7.1 Hz, 1 H), 4.47 - 4.58 (m, 1 H), 4.84 (s, 2 H), 6.32 (d, J=8.6 Hz, 1 H), 7.23 (d, J=8.1 Hz, 2 H), 7.30 (d, 1 H), 7.35 (t, J=7.7 Hz, 1 H), 7.44 (d, J=7.3 Hz, 1 H), 7.49 (d, J=8.1 Hz, 2 H), 7.54 (s, 1 H).

Example 1-15: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.48 - 2.59 (m, 3 H), 2.61 - 2.71 (m, 3 H), 2.91 - 3.06 (m, 8 H), 4.53 - 4.63 (m, 1 H), 4.67 (d, J=14.7 Hz, 1 H), 5.03 (d, J=14.7 Hz, 1 H), 7.30 (dt, J=7.8, 1.8 Hz, 1 H), 7.32 - 7.38 (m, 3 H), 7.45 (dt, J=7.6, 1.5 Hz, 1 H), 7.50 (d, J=8.1 Hz, 2 H), 7.55 (t, J=1.8 Hz, 1 H), 8.08 (d, J=9.3 Hz, 1 H).

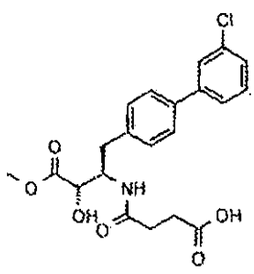
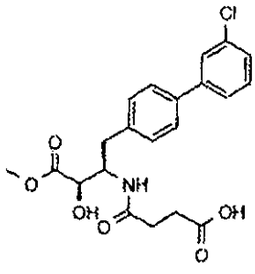
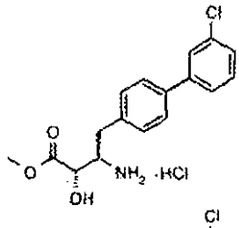
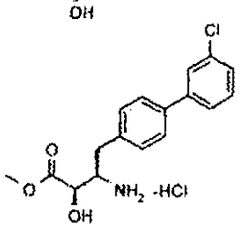
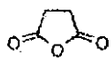
Example 1-16: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 - 2.32 (m, 2 H), 2.32 - 2.41 (m, 2 H), 2.42 - 2.50 (m, 1 H), 2.57 (dd, J=15.4, 5.6 Hz, 1 H), 2.80 (d, J=36.1 Hz, 2 H), 3.15 (br. s., 2 H), 3.31 - 3.50 (m, 4 H), 3.52 - 4.05 (m, 4 H), 4.25 - 4.40 (m, 3 H), 7.31 (d, J=8.3 Hz, 2 H), 7.39 - 7.43 (m, 1 H), 7.48 (t, J=7.8 Hz, 1 H), 7.60 - 7.67 (m, 3 H), 7.70 (t, J=1.8 Hz, 1 H), 8.02 (d, J=8.6 Hz, 1 H), 10.06 (br. s., 1 H), 12.17 (br. s., 1 H).

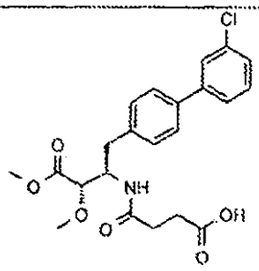
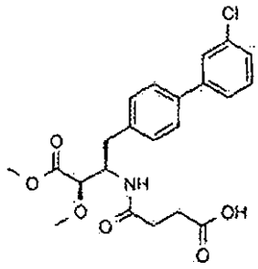
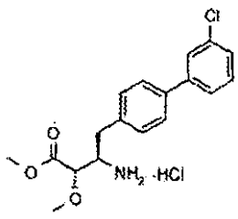
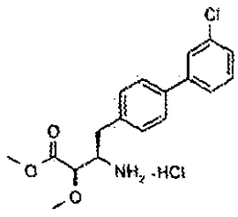
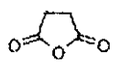
Example 1-17: Synthesis of (R)-4-(1-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid

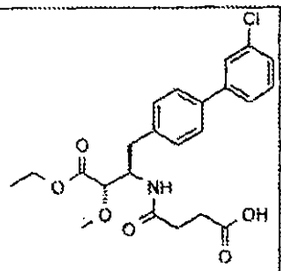
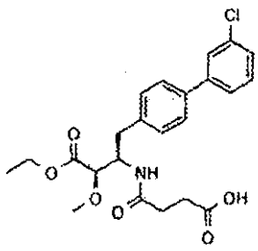
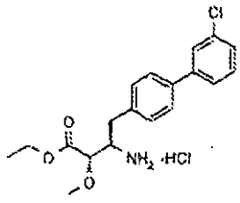
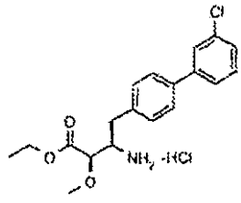
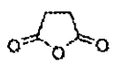
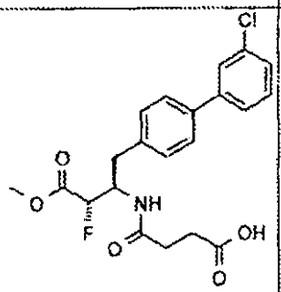
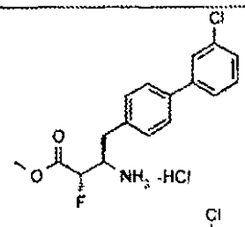
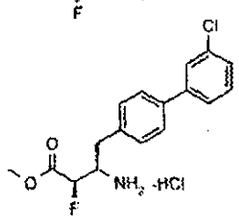
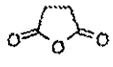


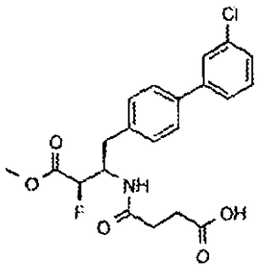
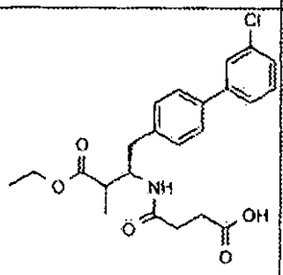
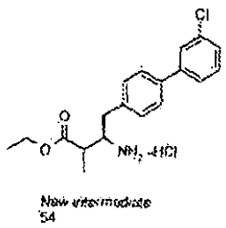
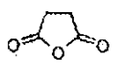
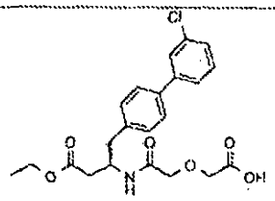
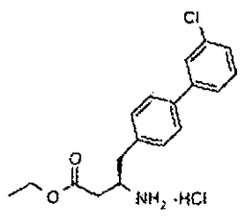
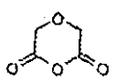
A solution of (*R*)-ethyl 3-amino-4-(5'-chloro-2'-fluorobiphenyl-4-yl)butanoate hydrochloride (293 mg, 0.777 mmol), succinic anhydride (93 mg, 0.932 mmol) and DIPEA (0.204 mL, 1.165 mmol) in dichloromethane (4 mL) is allowed to stir for 1.5 hours. The reaction is quenched with 1 M aqueous HCl and extracted with dichloromethane. The organic layer is separated and concentrated under reduced pressure. The resulting residue is purified by preparative HPLC using a gradient of 20% MeCN/water (0.1% TFA) to 100% MeCN to give (R)-4-(1-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid (294 mg). HPLC retention time = 1.03 minutes (condition B); MS (m+1) = 436.2; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, *J* = 7.07 Hz, 3 H) 2.46 - 2.58 (m, 4 H) 2.64 – 2.68 (m, 2 H) 2.87 (A of ABX, J_{ab} = 13.64 Hz, J_{ax} = 7.83 Hz, 1 H) 2.99 (B of ABX, J_{ab} = 13.64 Hz, J_{bx} = 6.57 Hz, 1 H) 4.11 – 4.22 (m, 2 H) 4.47 - 4.56 (m, 1 H) 6.60 (br d, *J* = 8.59 Hz, 1 H) 7.05 – 7.10 (m, 1 H) 7.23 - 7.27 (m, 3 H) 7.39 - 7.41 (m, 1 H) 7.44 - 7.46 (m, 2H).

Following compounds are prepared using similar procedure as described in example 1-17:

Example #	Product	Starting Meterial	Condition	HPLC-RT (condition)	MS (M+1)
Example 1-18	 (2S,3R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-hydroxy-butyric acid methyl ester  (2R,3R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-hydroxy-butyric acid methyl ester	  Intermediate 50	 Et_3N, DCM	1.29 min. (A)	420.0

Example 1-19	 (2S,3R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-methoxy-butyric acid methyl ester  (2R,3R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-methoxy-butyric acid methyl ester	  Intermediate 51	 DIPEA, DCM	1.21 min. (A)	434.2

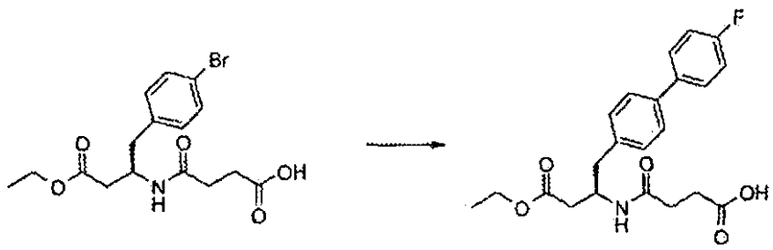
Example 1-20	 (2S,3R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-methoxy-butyric acid ethyl ester  (2R,3R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-methoxy-butyric acid ethyl ester	  Intermediate 52	 DIPEA, DCM	1.57 min. (A)	448.3
Example 1-21	 (2S,3R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-	  Intermediate 53	 Et_3N, DCM	0.83 min. (B)	422.1

	2-fluoro-butyric acid methy lester  (2R,3R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-fluoro-butyric acid methyl ester				
Example 1-22	 (R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-methyl-butyric acid ethyl ester	 New intermediate 54	 Et_3N, DCM	0.98 min. (B)	432
Example 1-23	 (R)-3-(2-Carboxymethoxy-acetylamino)-4-(3'-		 Et_3N, DCM	0.75 min. (B)	434

	chloro-biphenyl-4-yl)-butyric acid ethyl ester				

Example 1-20: 1H NMR (400 MHz, $CDCl_3$) δ ppm 1.15 (t, *J* = 7.07 Hz, 3 H), 2.24-2.34 (m, 4 H), 2.74 (dd, *J* = 8.59, 13.39 Hz), 2.88 (dd, *J* = 6.32, 13.39 Hz), 3.34 (s, 3H), 3.75 (d, *J* = 2.78 Hz, 1 H), 4.04 (dd, *J* = 7.07, 13.89 Hz, 2 H), 4.33-4.43 (m, 1 H), 7.31 (d, *J* = 8.08 Hz, 2 H), 7.38-7.43 (m, 1 H), 7.48 (t, *J* = 7.83 Hz, 1 H), 7.63 (d, *J* = 3.34 Hz), 7.71 (t, *J* = 1.77 Hz, 1 H), 7.95 (d, *J* = 9.35 Hz, 1 H).

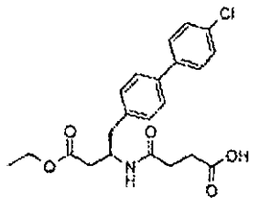
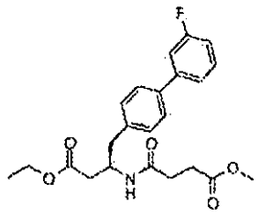
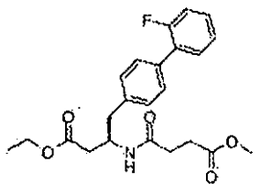
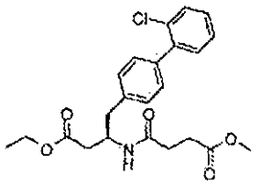
Example 2-1: Synthesis of (R)-3-(3-carboxy-propionylamino)-4-(4'-fluoro-biphenyl-4-yl)-butyric acid ethyl ester

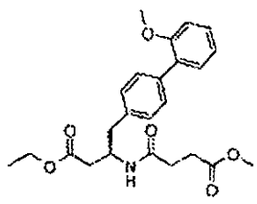
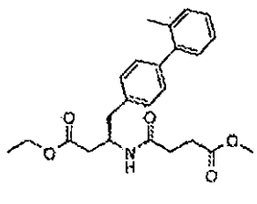
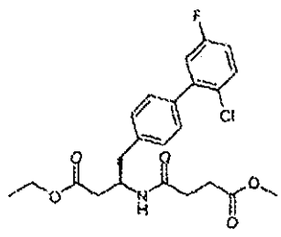
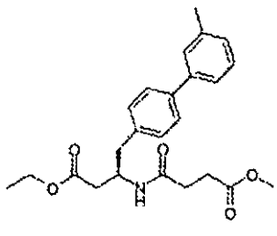


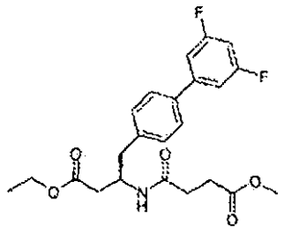
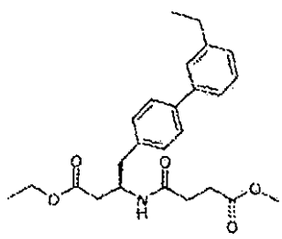
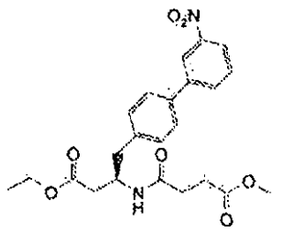
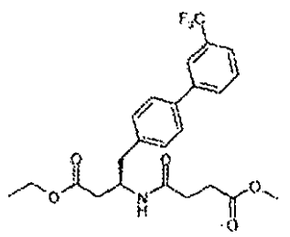
A mixture of (R)-4-(1-(4-bromophenyl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid (50 mg, 0.129 mmol), 4-fluorophenylboronic acid (27.2 mg, 0.194 mmol), $Pd(Ph_3P)_4$ (14.96 mg, 0.013 mmol) and aqueous Na2CO3 (0.129 mL, 0.259 mmol) in toluene (1 mL) is allowed to stir at 95 °C under nitrogen. After stirring for 13 hours, the solution is cooled to ambient temperature and then quenched with aqueous 1 M HCl. The products are extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained residue is purified by RP-HPLC (SunFire C18, H_2O(0.1% TFA)/CH_3CN), and then lyophilized to give (R)-3-(3-carboxy-propionylamino)-4-(4'-fluoro-biphenyl-4-yl)-butyric acid ethyl ester (29.2 mg). HPLC retention time = 1.26 minutes (condition B); MS (m+1) = 402.2; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J* = 7 Hz, 3 H) 2.47 – 2.67 (m, 6 H) 2.87 (A of ABX, Jab = 13.7 Hz, Jax = 7.9 Hz, 1 H) 2.99 (B of ABX, Jab = 13.7 Hz, Jbx = 6.6 Hz, 1 H) 4.12 – 4.23 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.52 (br d, J = 8.6 Hz, 1 H) 7.08 – 7.14 (m, 2 H) 7.24 (d, J = 8.4 Hz, 2 H) 7.46 – 7.55 (m, 4 H).

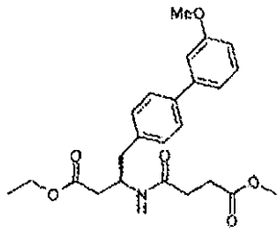
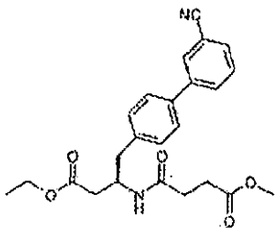
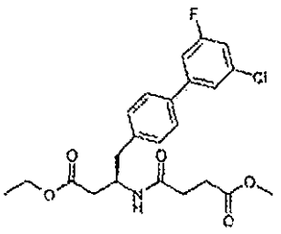
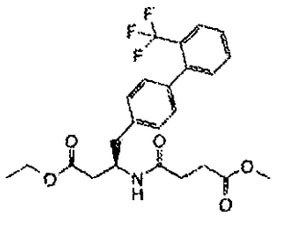
Following compounds are prepared using similar procedure as described in example 2-1:

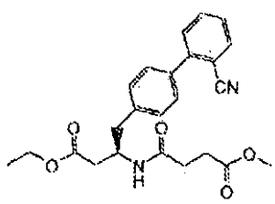
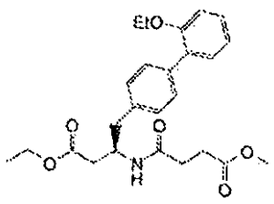
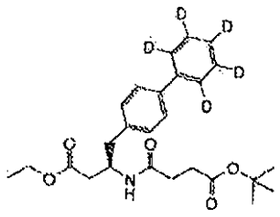
Example	Product	Reagent	HPLC-RT	MS (M+1)

			(condition)	
Example 2-2		$Pd(PPh_3)_4$, *p*-chlorophenylboronic acid, aq. 2M Na_2CO_3, (R)-4-(1-(4-bromophenyl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid	1.49 min. (B)	418.1
Example 2-3		$Pd(PPh_3)_4$, *m*-fluorophenylboronic acid, aq. 2M Na_2CO_3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.24 min. (B)	416.1
Example 2-4		$Pd(PPh_3)_4$, *o*-fluorophenylboronic acid, aq. 2M Na_2CO_3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.25 min. (B)	416.1
Example 2-5		$Pd(PPh_3)_4$, *o*-chlorophenylboronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.33 min. (B)	432.1

Example 2-6		$Pd(PPh_3)_4$, o-methoxyphenylboronic acid, aq. 2M Na_2CO_3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.22 min. (B)	428.2
Example 2-7		$Pd(PPh_3)_4$, o-tolylboronic acid, aq. 2M Na_2CO_3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.35 min. (B)	412.2
Example 2-8		Pd(PPh3)4, 2-chloro-5-fluorophenylboronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.28 min. (B)	450.3
Example 2-9		Pd(PPh3)4, m-tolylboronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.28 min. (B)	412.2

Example 2-10		Pd(PPh3)4, 3,5-difluorophenylboronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.23 min. (B)	434.2
Example 2-11		Pd(PPh3)4, 3-ethylphenylboronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.40 min. (B)	426.3
Example 2-12		Pd(PPh3)4, 3-nitrophenylboronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.16 min. (B)	443.2
Example 2-13		Pd(PPh3)4, 3-(trifluoromethyl)phenyl boronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.39 min. (G)	466.1

Example 2-14		Pd(PPh3)4, 3-methoxyphenylboronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.19 min. (G)	428.2
Example 2-15		Pd(PPh3)4, 3-cyanobenzeneboronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	0.98 min. (B)	423.2
Example 2-16		Pd(PPh3)4, 3-chloro-5-fluorophenylboronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.45 min. (B)	450.1
Example 2-17		Pd(PPh3)4, 2-(trifluoromethyl)phenylboronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-	1.37 min. (B)	466.1

		oxobutanamido)butanoate.		
Example 2-18		Pd(PPh3)4, 2-cyanophenylboronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.01 min. (B)	423.2
Example 2-19		Pd(PPh3)4, 2-ethoxyphenylboronic acid, aq. 2M Na2CO3, (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate.	1.29 min. (B)	442.2
Example 2-20		PdCl2(dppf).CH2Cl2 complex, phenyl-d5-boronic acid, aq. 2M Na2CO3, (R)-tert-butyl 4-(1-(4-bromophenyl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoate	1.42 min. (B)	445.2

Example 2-2: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, J = 7 Hz, 3 H) 2.47 – 2.67 (m, 6 H) 2.84 – 3.02 (m, 2 H) 4.12 – 4.24 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.52 (br d, J = 9.3 Hz, 1 H) 7.24 – 7.26 (m, 2 H) 7.39 – 7.41 (m, 2 H) 7.48 – 7.51 (m, 4 H).

Example 2-3: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, J = 7 Hz, 3 H) 2.43 – 2.65 (m, 6 H) 2.84 – 3.02 (m, 2 H) 3.67 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.30 (br d, J = 8.6 Hz, 1 H) 7.00 – 7.05 (m, 1 H) 7.26 – 7.29 (m, 3 H) 7.34 – 7.41 (m, 2 H) 7.51 (d, J= 8.3 Hz, 2 H).

Example 2-4: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, J = 7 Hz, 3 H) 2.44 – 2.65 (m, 6 H) 2.85 – 3.02 (m, 2 H) 3.67 (s, 3 H) 4.11 – 4.23 (m, 2 H) 4.48 – 4.56 (m, 1 H) 6.30 (br d, J = 9.6 Hz, 1 H) 7.11 – 7.22 (m, 2 H) 7.25 – 7.33 (m, 3 H) 7.40 – 7.45 (m, 1 H) 7.48 – 7.50 (m, 2 H).

Example 2-5: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, J = 7.2 Hz, 3 H) 2.44 – 2.65 (m, 6 H) 2.86 – 3.02 (m, 2 H) 3.68 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.49 – 4.57 (m, 1 H) 6.31 (br d, J = 8.8 Hz, 1 H) 7.24 – 7.34 (m, 5 H) 7.37 – 7.39 (m, 2 H) 7.45 – 7.47 (m, 1 H).

Example 2-6: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, J = 7 Hz, 3 H) 2.44 – 2.66 (m, 6 H) 2.84 – 3.01 (m, 2 H) 3.68 (s, 3 H) 3.81 (s, 3 H) 4.11 – 4.23 (m, 2 H) 4.48 – 4.56 (m, 1 H) 6.26 (br d, J = 8.8 Hz, 1 H) 6.97 – 7.04 (m, 2 H) 7.22 (d, J = 8.1 Hz, 2 H) 7.29 – 7.33 (m, 2 H) 7.46 – 7.48 (m, 2 H).

Example 2-7: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, J = 7.1 Hz, 3 H) 2.26 (s, 3 H) 2.44 – 2.69 (m, 6 H) 2.85 – 3.01 (m, 2 H) 3.68 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.48 – 4.57 (m, 1 H) 6.30 (br d, J = 8.6 Hz, 1 H) 7.21 – 7.26 (m, 8 H).

Example 2-8: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J* = 7.2 Hz, 3 H) 2.44 – 2.69 (m, 6 H) 2.86 – 3.03 (m, 2 H) 3.68 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.48 – 4.57 (m, 1 H) 6.31 (br d, *J* = 8.8 Hz, 1 H) 6.90 – 7.01 (m, 1 H) 7.05 – 7.08 (m, 1 H) 7.25 – 7.27 (m, 2 H) 7.36 – 7.43 (m, 3 H).

Example 2-9: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, *J* = 7.2 Hz, 3 H) 2.41 – 2.65 (m, 9 H) 2.84 – 3.00 (m, 2 H) 3.67 (s, 3 H) 4.11 – 4.23 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.29 (br d, *J* = 8.9 Hz, 1 H) 7.16 – 7.39 (m, 6 H) 7.50 – 7.53 (m, 2 H).

Example 2-10: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J* = 7.2 Hz, 3 H) 2.43 – 2.65 (m, 6 H) 2.84 – 3.02 (m, 2 H) 3.67 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.46 – 4.55 (m, 1 H)

6.33 (br d, *J* = 8.8 Hz, 1 H) 6.76 – 6.80 (m, 1 H) 7.06 – 7.12 (m, 2 H) 7.26 – 7.27 (m, 2 H) 7.48 (d, *J* = 8.0 Hz, 2 H).

Example 2-11: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.27 – 1.30 (m, 6 H) 2.44 – 2.57 (m, 4 H) 2.62 – 2.74 (m, 4 H) 2.84 – 3.00 (m, 2 H) 3.67 (s, 3 H) 4.13 – 4.23 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.30 (br d, J = 7.6 Hz, 1 H) 7.17 – 7.26 (m, 3 H) 7.33 – 7.41 (m, 3 H) 7.52 (d, *J* = 7.8 Hz, 2 H).

Example 2-12: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.30 (t, *J* = 7.1 Hz, 3 H) 2.41 – 2.65 (m, 6 H) 2.67 – 2.92 (m, 1 H) 3.00 – 3.05 (m, 1 H) 3.68 (s, 3 H) 4.14 – 4.22 (m, 2 H) 4.48 – 4.56 (m, 1 H) 6.33 (br d, *J* = 8.6 Hz, 1 H) 7.32 (d, *J* = 8.3 Hz, 2 H) 7.56 – 7.62 (m, 3 H) 7.89 – 7.91 (m, 1 H) 8.18 – 8.20 (m, 1 H) 8.44 (t, *J* = 8.0 Hz, 1 H).

Example 2-13: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J* = 7.2 Hz, 3 H) 2.44 – 2.65 (m, 6 H) 2.86 – 2.91 (m, 1 H) 2.98 – 3.03 (m, 1 H) 3.67 (s, 3 H) 4.13 – 4.22 (m, 2 H) 4.47 – 4.56 (m, 1 H) 6.33 (br d, *J* = 8.8 Hz, 1 H) 7.29 (d, *J* = 8.2 Hz, 2 H) 7.53 (d, *J* = 8.2 Hz, 2 H) 7.56 – 7.60 (m, 2 H) 7.75 (d, *J* = 7.6 Hz, 1 H) 7.81 (s, 1 H).

Example 2-14: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, *J* = 7.2 Hz, 3 H) 2.43 – 2.65 (m, 6 H) 2.84 – 2.89 (m, 1 H) 2.96 – 3.01 (m, 1 H) 3.67 (s, 3 H) 3.86 (s, 3 H) 4.11 – 4.23 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.30 (br d, *J* = 8.8 Hz, 1 H) 6.87 – 6.90 (m, 1 H) 7.10 – 7.11 (m, 1 H) 7.15 – 7.17 (m, 1 H) 7.24 – 7.26 (m, 2 H) 7.34 (t, *J* = 7.8 Hz, 2 H) 7.51 – 7.53 (m, 2 H).

Example 2-15: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J* = 7.1 Hz, 3 H) 2.43 – 2.58 (m, 4 H) 2.61 – 2.65 (m, 2 H) 2.84 – 2.91 (m, 1 H) 2.98 – 3.03 (m, 1 H) 3.68 (s, 3 H) 4.12 – 4.24 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.34 (br d, *J* = 8.8 Hz, 1 H) 7.30 (d, *J* = 8.1 Hz, 2 H) 7.50 (d, *J* = 8.1 Hz, 2 H) 7.51 – 7.63 (m, 2 H) 7.78 – 7.81 (m, 1 H) 7.85 (br s, 1 H).

Example 2-16: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J* = 7.1 Hz, 3 H) 2.43 – 2.57 (m, 4 H) 2.61 – 2.64 (m, 2 H) 2.87 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.99 (B of ABX, J_{ab} = 13.6 Hz; J_{bx} = 6.6 Hz, 1 H) 3.68 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.46 – 4.55 (m, 1 H) 6.34 (br d, *J* = 8.6 Hz, 1 H) 7.05 (dt, *J* = 8.3 and 2.0 Hz, 1 H) 7.15 – 7.19 (m, 1 H) 7.26 – 7.28 (m, 3 H) 7.35 – 7.36 (m, 1 H) 7.45 (d, *J* = 8.1 Hz, 2 H).

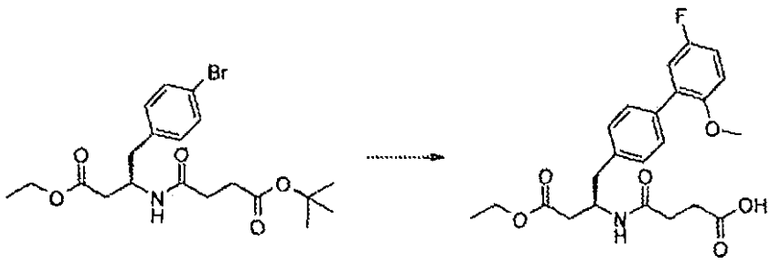
Example 2-17: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J* = 7.1 Hz, 3 H) 2.43 – 2.69 (m, 6 H) 2.90 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.99 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.8 Hz, 1 H) 3.68 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.49 – 4.57 (m, 1 H) 6.31 (br d, *J* = 8.6 Hz, 1 H) 7.20 – 7.26 (m, 4 H) 7.32 (d, *J* = 7.6 Hz, 1 H) 7.44 – 7.47 (m, 1 H) 7.53 – 7.57 (m, 1 H) 7.73 (d, *J* = 7.6 Hz, 2 H).

Example 2-18: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J* = 7.2 Hz, 3 H) 2.44 – 2.65 (m, 6 H) 2.91 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 3.01 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.6 Hz, 1 H) 3.68 (s, 3 H) 4.12 – 4.24 (m, 2 H) 4.48 – 4.57 (m, 1 H) 6.34 (br d, *J* = 8.6 Hz, 1 H) 7.32 (d, *J* = 8.1 Hz, 2 H) 7.41 – 7.56 (m, 2 H) 7.62 – 7.66 (m, 1 H) 7.75 – 7.77 (m, 1 H) 7.81 – 7.84 (m, 2 H).

Example 2-19: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, *J* = 7.2 Hz, 3 H) 1.35 (t, *J* = 6.9 Hz, 3 H) 2.44 – 2.53 (m, 4 H) 2.44 – 2.53 (m, 4 H) 2.86 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.1 Hz, 1 H) 2.98 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.1 Hz, 1 H) 3.67 (s, 3 H) 3.99 – 4.23 (m, 4 H) 4.48 – 4.56 (m, 1 H) 6.27 (br d, *J* = 8.6 Hz, 1 H) 6.94 – 7.04 (m, 2 H) 7.20 – 7.22 (m, 2 H) 7.27 – 7.33 (m, 2 H) 7.41 – 7.52 (m, 2 H).

Example 2-20: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, *J* = 7.2 Hz, 3 H) 1.43 (s, 9 H) 2.36 –2.56 (m, 6 H) 2.84 – 3.01 (m, 4 H) 4.11 – 4.22 (m, 2 H) 4.47 – 4.56 (m, 1 H) 6.30 – 6.35 (m, 1 H) 7.25 – 7.27 (m, 2 H) 7.51 – 7 .54 (m, 2 H).

Example 2-21: Synthesis of (R)-4-(4-ethoxy-1-(5'-fluoro-2'-methoxybiphenyl-4-yl)-4-oxobutan-2-ylamino)-4-oxobutanoic acid

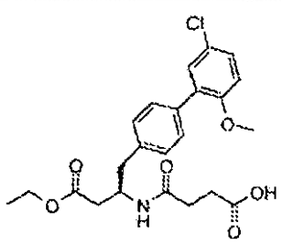


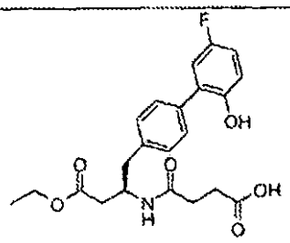
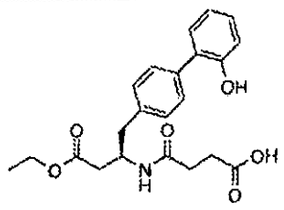
To a solution of (R)-tert-butyl 4-(1-(4-bromophenyl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoate, intermediate 9, (100 mg, 0.23 mmol) and 5-fluoro-2-methoxyphenylboronic acid (57.6 mg, 0.34 mmol) in toluene (1 mL) and EtOH (0.1 mL) is added $Pd(PPh_3)_4$ (26.1

mg, 0.023 mmol) and Na_2CO_3 (47.9 mg, 0.45 mmol). After stirring at 95 °C under nitrogen for 18 hours, the solution is cooled to ambient temperature and then quenched with aqueous 1 M HCl. The crude is diluted with ethyl acetate, the organic layer is washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue is purified by flash column chromatography on silica gel (eluent: heptane/EtOAc = 100:0 to 30:70) to give (R)-tert-butyl 4-(4-ethoxy-1-(5'-fluoro-2'-methoxybiphenyl-4-yl)-4-oxobutan-2-ylamino)-4-oxobutanoate (65 mg). HPLC retention time = 1.44 minutes (condition B); MS (m+1) = 488.3; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.32 (t, *J*=7.1 Hz, 3 H) 1.48 (s, 9 H) 2.41 - 2.48 (m, 2 H) 2.51 - 2.63 (m, 4 H) 2.90 (dd, *J*=13.6, 6 Hz, 1 H) 3.02 (dd, *J*=13.6, 6 Hz, 1 H) 3.81 (s, 3 H) 4.14 - 4.29 (m, 2 H) 4.49 - 4.63 (m, 1 H) 6.44 (d, *J*=8.6 Hz, 1 H) 6.89 - 6.97 (m, 1 H) 6.98 - 7.05 (m, 1 H) 7.05 - 7.11 (m, 1 H) 7.27 (d, *J*=8.1 Hz, 2 H) 7.49 (d, *J*=8.1 Hz, 2 H).

A solution of (R)-tert-butyl 4-(4-ethoxy-1-(5'-fluoro-2'-methoxybiphenyl-4-yl)-4-oxobutan-2-ylamino)-4-oxobutanoate, (65 mg, 0.13 mmol) in 4M HCl in 1,4-dioxane (671 µL, 2.68 mmol) is stirred at room temperature. After stirring for 1 hour, the reaction mixture is concentrated under reduced pressure. The obtained residue is purified by RP-HPLC (SunFire C18, H_2O(0.1% TFA)/CH_3CN), and then lyophilized to give (R)-4-(4-ethoxy-1-(5'-fluoro-2'-methoxybiphenyl-4-yl)-4-oxobutan-2-ylamino)-4-oxobutanoic acid (23 mg). HPLC retention time = 1.66 minutes (condition D); MS (m+1) = 432.3; 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (t, *J*=7.1 Hz, 3 H) 2.21 - 2.32 (m, 2 H) 2.32 - 2.40 (m, 2 H) 2.40 - 2.48 (m, 2 H) 2.77 (d, *J*=6.8 Hz, 2 H) 3.74 (s, 3 H) 4.03 (q, *J*=7.1 Hz, 2 H) 4.19 - 4.33 (m, 1 H) 7.04 - 7.20 (m, 3 H) 7.23 (d, *J*=8.1 Hz, 2 H) 7.43 (d, *J*=8.1 Hz, 2 H) 7.93 (d, *J*=8.3 Hz, 1 H)

Following compounds are prepared using similar procedure as described in example 2-21:

Example	Product	Reagent	LCMS-RT (condition)	MS (M+1)
Example 2-22		$Pd(PPh_3)_4$, 5-chloro-2-methoxyphenylboronic acid, aq. 2M Na_2CO_3, (R)-tert-butyl 4-(1-(4-bromophenyl)-	1.63 min. (D)	448.2

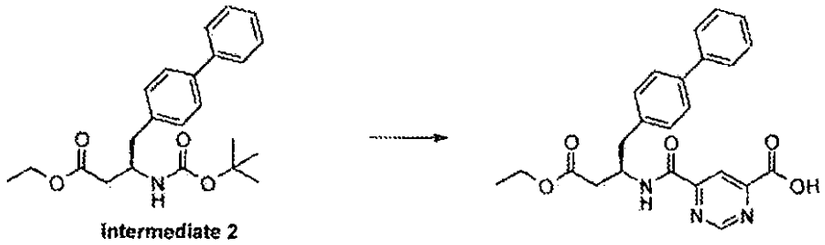
	(R)-4-(1-(5'-chloro-2'-methoxybiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid	4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoate.		
Example 2-23	 (R)-4-(4-ethoxy-1-(5'-fluoro-2'-hydroxybiphenyl-4-yl)-4-oxobutan-2-ylamino)-4-oxobutanoic acid	$Pd(PPh_3)_4$, 5-fluoro-2-hydroxyphenylboronic acid, aq. 2M Na_2CO_3, (R)-tert-butyl 4-(1-(4-bromophenyl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoate.	1.29 min (A)	418.3
Example 2-24	 (R)-4-(4-ethoxy-1-(2'-hydroxybiphenyl-4-yl)-4-oxobutan-2-ylamino)-4-oxobutanoic acid	$Pd(PPh_3)_4$, 2-hydroxyphenylboronic acid, aq. 2M Na_2CO_3, (R)-tert-butyl 4-(1-(4-bromophenyl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoate.	1.65 min (D)	400.3

Example 2-22: 1H NMR (400 MHz, CD_3OD) δ ppm 1.23 (t, *J*=7.1 Hz, 3 H) 2.36 - 2.58 (m, 6 H) 2.85 (d, *J*=7.1 Hz, 2 H) 3.76 (s, 3 H) 4.10 (q, *J*=7.1 Hz, 2 H) 4.40 - 4.57 (m, 1 H) 7.01 (d, *J*=8.6 Hz, 1 H) 7.17 - 7.30 (m, 4 H) 7.39 (d, *J*=8.1 Hz, 2 H)

Example 2-23: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (t, *J*=7.2 Hz, 1 H) 2.23 - 2.30 (m, 2 H) 2.34 - 2.40 (m, 2 H) 2.40 - 2.45 (m, 2 H) 2.75 (dd, *J*=6.6, 3.3 Hz, 2 H) 4.02 (q, *J*=7.2 Hz, 2 H) 4.19 - 4.30 (m, 1 H) 6.87 - 6.94 (m, 1 H) 6.93 - 7.02 (m, 1 H) 7.07 (dd, *J*=9.7, 3.2 Hz, 1 H) 7.22 (d, *J*=8.1 Hz, 2 H) 7.49 (d, *J*=8.1 Hz, 2 H) 7.94 (d, *J*=8.1 Hz, 1 H) 9.52 (s, 1 H)

Example 2-24: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (t, *J*=7.1 Hz, 3 H) 2.22 - 2.32 (m, 2 H) 2.34 - 2.41 (m, 2 H) 2.43 (dd, *J*=6.8, 3.3 Hz, 2 H) 2.68 - 2.82 (m, 2 H) 4.02 (q, *J*=7.1 Hz, 2 H) 4.17 - 4.35 (m, 1 H) 6.80 - 6.89 (m, 1 H) 6.93 (d, *J*=7.1 Hz, 1 H) 7.09 - 7.17 (m, 1 H) 7.17 - 7.29 (m, 3 H) 7.46 (d, *J*=8.3 Hz, 2 H) 7.93 (d, *J*=8.1 Hz, 1 H) 9.46 (br. s., 1 H)

Example 3-1: Syntheis of (R)-6-(1-(biphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylcarbamoyl)pyrimidine-4-carboxylic acid

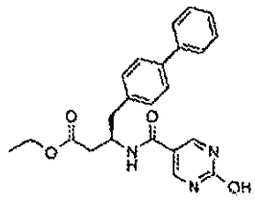
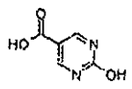
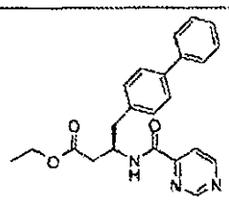
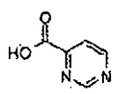
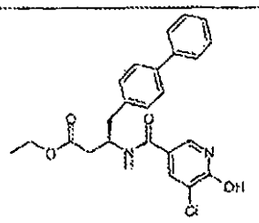
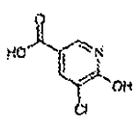


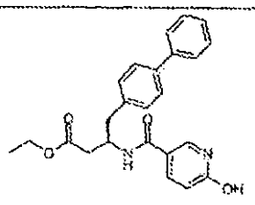
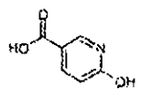
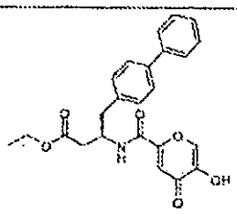
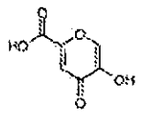
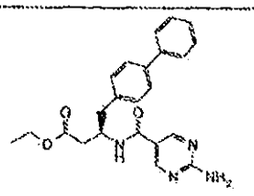
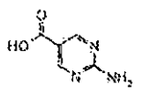
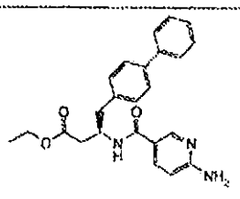
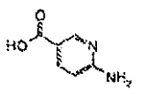
intermediate 2

To (*R*)-ethyl-4-(biphenyl-4-yl)-3-(*tert*-butoxycarbonylamino)butanoate (300 mg, 0.782 mmol) is added a solution of 4M HCl in 1,4-dioxane (3.92 mL, 15.65 mmol) at room temperature. After stirring for 1 hour, the reaction mixture is concentrated under reduced pressure to give (*R*)-3-amino-4-biphenyl-4-yl-butyric acid ethyl ester hydrochloride.

Next, to a suspension of pyrimidine-4,6-dicarboxylic acid (325 mg, 1.935 mmol), (*R*)-3-amino-4-biphenyl-4-yl-butyric acid ethyl ester hydrochloride (250 mg, 0.774 mmol), WSC hydrochloride (148 mg, 0.774 mmol) and HOAt (105 mg, 0.774 mmol) in DMF (4 mL) and H_2O (1 mL) is added DIPEA (0.135 mL, 0.774 mmol). After stirring for 14 hours, the reaction is quenched with H2O, and the products are extracted with EtOAc, washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure.
The obtained residue is purified by RP-HPLC (SunFire C18, H_2O(0.1% TFA)/CH_3CN), and then lyophilized to give (R)-6-(1-(biphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylcarbamoyl)pyrimidine-4-carboxylic acid (84.8 mg). HPLC retention time = 1.32 minutes (condition B); MS (m+1) = 434.1; 1H NMR (400 MHz, DMSO-*d6*) δ ppm 1.12 (t, J = 7.0 Hz, 3 H) 2.65 (A of ABX, Jab = 15.4 Hz, Jax = 5.8 Hz, 1 H) 2.73 (B of ABX, Jab = 15.4 Hz, Jbx = 7.9 Hz) 2.91 (A of ABX, Jab = 13.6 Hz, Jax = 6.1 Hz, 1 H) 3.01 (B of ABX, Jab = 13.6 Hz, Jbx = 8.2 Hz, 1 H) 4.01 (q, J = 7.0 Hz, 2 H) 4.59 – 4.68 (m, 1 H) 7.29 – 7.35 (m, 3 H) 7.41 – 7.45 (m, 2 H) 7.55 – 7.63 (m, 4 H) 8.32 (d, J = 1.35 Hz, 1 H) 9.19 (d, J = 9.1 Hz, 1 H) 9.50 (d, J = 1.35 Hz, 1 H) 14.11 (br s, 1 H).

Following compounds are prepared using similar procedure as described in example 3-1:

Example #	Product	Reagent	HPLC-RT (condition)	MS (M+1)
Example 3-2	 (R)-4-biphenyl-4-yl-3-[(2-hydroxy-pyrimidine-5-carbonyl)-amino]-butyric acid ethyl ester		1.56 min. (A)	406.2
Example 3-3	 (R)-4-biphenyl-4-yl-3-[(pyrimidine-4-carbonyl)-amino]-butyric acid ethyl ester		1.73 min. (A)	390
Example 3-4	 (R)-ethyl 4-(biphenyl-4-yl)-3-(5-chloro-6-hydroxynicotinamido)butanoate	 PyBOP instead of WSC.HCl and HOAt	1.69 min. (D)	439.0

Example 3-5	 (R)-ethyl 4-(biphenyl-4-yl)-3-(6-hydroxynicotinamido)butanoate	 PyBOP instead of WSC.HCl, HOAt	1.55 min. (B)	405.2
Example 3-6	 (R)-ethyl 4-(biphenyl-4-yl)-3-(5-hydroxy-4-oxo-4H-pyran-2-carboxamido)butanoate		1.65 min. (A)	422.2
Example 3-7	 (R)-ethyl 3-(2-aminopyrimidine-5-carboxamido)-4-(biphenyl-4-yl)butanoate	 PyBOP instead of WSC.HCl and HOAt	1.58 min. (A)	405.8
Example 3-8	 (R)-ethyl 3-(6-aminonicotinamido)-4-(biphenyl-4-yl)butanoate	 PyBOP instead of WSC.HCl and HOAt	1.65 min. (A)	404.3

Example 3-2: 1H NMR (400 MHz, DMSO-*d6*) δ ppm 1.14 (t, J = 7.1 Hz, 3 H) 2.57 (d, J = 7.1 Hz, 2 H) 2.83 – 2.92 (m, 2 H) 4.03 (q, J = 7.1 Hz, 2 H) 4.43 – 4.52 (m, 1 H) 7.29 – 7.36 (m, 3 H) 7.42 – 7.46 (m, 2 H) 7.58 – 7.65 (m, 4 H) 8.30 (d, J = 8.4 Hz, 1 H) 8.64 (br s, 1 H).

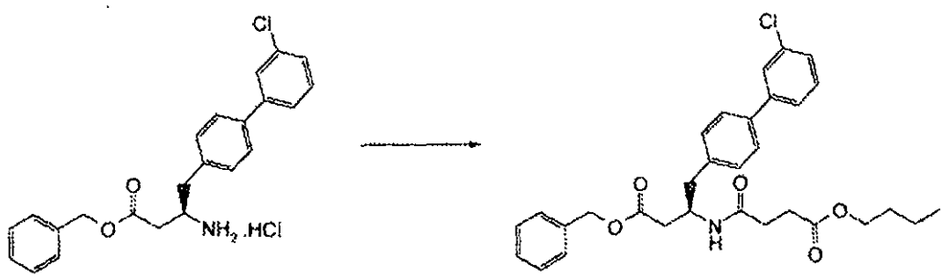
Example 3-4: 1H NMR (400 MHz, DMSO-*d6*) δ ppm 1.13 (t, J = 7.1 Hz, 3 H) 2.55 (d, J = 6.9 Hz, 2 H) 2.82 – 2.92 (m, 2 H) 4.00 (q, J = 7.1 Hz, 2 H) 4.43 – 4.52 (m, 1 H) 7.29 – 7.35 (m, 3 H) 7.42 – 7.46 (m, 2 H) 7.58 – 7.65 (m, 4 H) 7.93 – 7.96 (m, 1H) 8.10 (d, J = 2.3 Hz, 1 H) 8.25 (d, J = 8.3 Hz, 1 H) 12.53 (d, J = 6.1 Hz, 1 H).

Example 3-5: 1H NMR (400 MHz, DMSO-*d6*) δ ppm 1.13 (t, J = 7.1 Hz, 3 H) 2.55 (d, J = 7.6 Hz, 2 H) 2.81– 2.92 (m, 2 H) 4.02 (q, J = 7.1 Hz, 2 H) 4.43 – 4.52 (m, 1 H) 7.29 – 7.36 (m, 3 H) 7.42 – 7.46 (m, 2 H) 7.57 – 7.65 (m, 4 H) 7.78 – 7.81 (m, 1H) 7.92 (d, J = 2.3 Hz, 1 H) 8.16 (d, J = 8.1 Hz, 1 H) 11.92 (s, 1 H).

Example 3-6: 1H NMR (400 MHz, DMSO-*d6*) δ ppm 1.13 (t, J = 7 Hz, 3 H) 2.55 – 2.67 (m, 2 H) 2.83– 2.94 (m, 2 H) 4.02 (q, J = 7 Hz, 2 H) 4.46 – 4.55 (m, 1 H) 6.82 (s, 1 H) 7.28 - 7.35 (m, 3 H) 7.42 – 7.46 (m ,2 H) 7.59 (d, J = 8.3 Hz, 2 H) 7.63 (d, J = 7.0 Hz, 2 H) 8.13 (s, 1 H) 8.89 (d, J = 8.6 Hz, 1 H) 9.56 (s, 1 H).

Example 3-7: 1H NMR (400 MHz, DMSO-*d6*) δ ppm 1.13 (t, J = 7 Hz, 3 H) 2.56 – 2.58 (m, 2 H) 2.83– 2.94 (m, 2 H) 4.02 (q, J = 7 Hz, 2 H) 4.46 – 4.55 (m, 1 H) 7.19 (s, 2 H) 7.30 - 7.35 (m, 3 H) 7.42 – 7.46 (m ,2 H) 7.58 – 7.65 (m, 4H) 8.22 (d, J = 8.1 Hz, 1 H) 8.60 (s, 1 H).

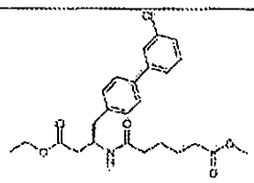
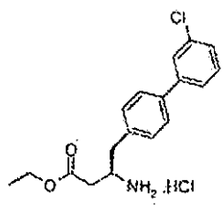
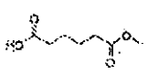
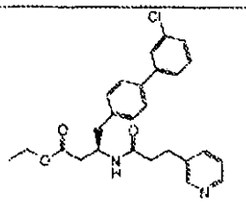
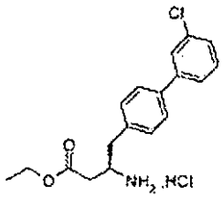
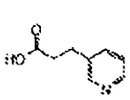
Example 3-9: Synthesis of (R)-benzyl 3-(4-butoxy-4-oxobutanamido)-4-(3'-chlorobiphenyl-4-yl)butanoate

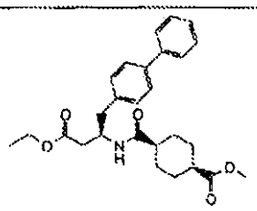
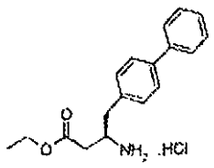
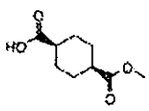
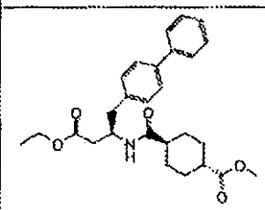
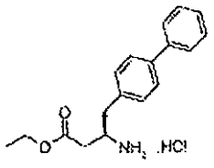
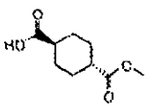
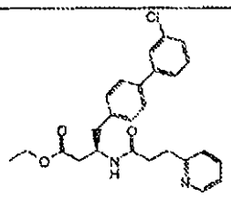
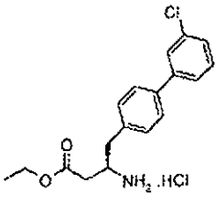
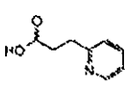


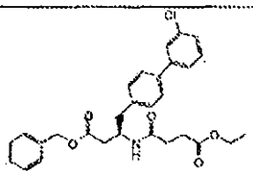
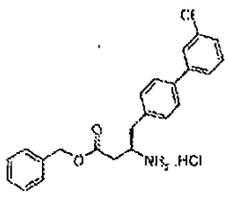
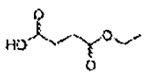
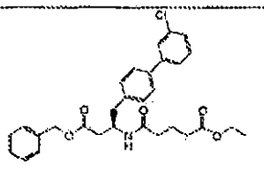
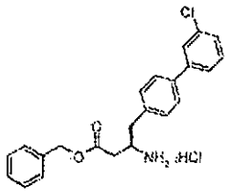
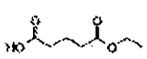
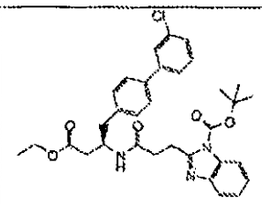
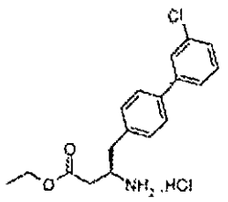
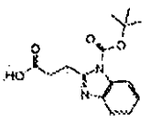
A mixture of (R)-benzyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride (150 mg, 0.360 mmol), 4-butoxy-4-oxobutanoic acid (107 mg, 0.540 mmol, 88% purity), EDCI (104

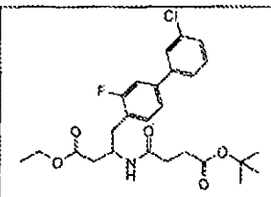
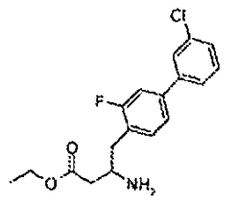
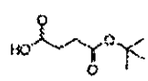
mg, 0.540 mmol), DIPEA (0.094 ml, 0.540 mmol) and HOAt (73.6 mg, 0.540 mmol) in DMF (2 ml) is allowed to stir at room temperature for 1 hour. The reaction mixture is diluted with water, and then the precipitated solid is collected on a funnel, washed with H2O, and dried under reduced pressure to give crude. The obtained residue is purified by silica gel flash column chromatography (heptane/EtOAc = 100:0 to 0:100) to give (R)-benzyl 3-(4-butoxy-4-oxobutanamido)-4-(3'-chlorobiphenyl-4-yl)butanoate (178.9 mg); HPLC retention time = 1.47 minutes (condition B); MS (m+1) = 536.42; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.90 – 0.94 (m, 3 H) 1.31 – 1.40 (m, 2 H) 1.56 – 1.63 (m, 2 H) 2.39 – 2.42 (m, 2 H) 2.48 – 2.62 (m, 4 H) 2.84 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.1 Hz, 1 H) 2.97 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.6 Hz, 1 H) 4.07 (t, *J* = 6.7 Hz, 2 H) 4.48 – 4.56 (m, 1 H) 5.12 (A of AB, *J* = 12.1 Hz, 1 H) 5.18 (B of AB, *J* = 12.1 Hz, 1 H) 6.27 (br d, *J* = 7.7 Hz, 1 H) 7.20 (d, *J* = 8.3 Hz, 1 H) 7.29 – 7.39 (m, 7 H) 7.42 – 7.47 (m, 3 H) 7.54 – 7.55 (m, 1 H).

Following compounds are prepared using similar procedure as described in example 3-8:

Example #	Product	Starting Material	Condition	HPLC-RT (condition)	MS (M+1)
Example 3-10	 (R)-methyl 6-(1-(3'-chlorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-6-oxohexanoate		 EDCI, HOAt, DIPEA, DMF, RT	1.40 min. (B)	460.5
Example 3-11	 (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(3-(pyridin-3-yl)propanamido)buta		 EDCI, HOAt, DMF, RT	1.56 min. (A)	451.3

	noate				
Example 3-12	 (1S,4s)-methyl 4-((R)-1-(biphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylcarbamoyl)cyclohexanecarboxylate		 EDCI, HOAt, DIPEA, DMF, RT	1.42 min. (B)	452.2
Example 3-13	 (1R,4r)-methyl 4-((R)-1-(biphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylcarbamoyl)cyclohexanecarboxylate		 EDCI, HOAt, DIPEA, DMF, RT	1.42 min. (B)	452.3
Example 3-14	 (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(3-(pyridin-2-yl)propanamido)butanoate		 EDCI, HOAt, DIPEA, DMF, RT	1.61 min. (A)	451.3

Example 3-16	 (R)-benzyl 4-(3'-chlorobiphenyl-4-yl)-3-(4-ethoxy-4-oxobutanamido)butanoate		 EDCI, HOAt, DIPEA, DMF, RT	1.56 min. (B)	508.3
Example 3-17	 (R)-ethyl 5-(4-(benzyloxy)-1-(3'-chlorobiphenyl-4-yl)-4-oxobutan-2-ylamino)-5-oxopentanoate		 EDCI, HOAt, DIPEA, DMF, RT	1.57 min. (B)	522.4
Example 3-18	 (R)-tert-butyl 2-(3-(1-(3'-chlorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-3-oxopropyl)-1H-benzo[d]imidazole-1-carboxylate		 EDCI, HOAt, DIPEA, THF, RT	0.80 min. (B)	590.3

Example 3-19	 tert-butyl 4-(1-(3'-chloro-3-fluorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoate		 EDCI, HOAt, DMF, RT	1.46 min. (B)	492.5

Example 3-10: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.29 (t, J = 7.2 Hz, 3 H) 1.58 – 1.64 (m, 4 H) 2.14 – 2.18 (m, 2 H) 2.28 – 2.32 (m, 2 H) 2.49 (A of ABX, J_{ab} = 16.2 Hz, J_{ax} = 5.3 Hz, 1 H) 2.53 (B of ABX, J_{ab} = 16.2 Hz, J_{bx} = 5.3 Hz, 1 H) 2.87 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.1 Hz, 1 H) 2.99 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.8 Hz, 1 H) 3.65 (s, 3 H) 4.11 - 4.23 (m, 2 H) 4.48 - 4.56 (m, 1 H) 6.18 (br d, J = 8.8 Hz, 1 H) 7.26 - 7.37 (m, 4 H) 7.43 – 7.52 (m, 3 H) 7.56 (br t, J = 1.8 Hz, 1 H)

Example 3-11: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.27 (t, J = 7.1 Hz, 3 H) 2.40 – 2.51 (m, 4 H) 2.77 – 2.83 (m, 1 H) 2.91 – 2.97 (m, 3 H) 4.08 - 4.20 (m, 2 H) 4.46 - 4.54 (m, 1 H) 6.22 – 6.24 (m, 1 H) 7.18 - 7.23 (m, 3 H) 7.29 - 7.37 (m, 2 H) 7.43 - 7.49 (m, 3 H) 7.55 – 7.57 (m, 2 H) 8.44 (d, J = 4.8 Hz, 1 H) 8.48 (s, 1 H).

Example 3-12: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.29 (t, J = 7.1 Hz, 3 H) 1.53 – 2.20 (m, 9 H) 2.46 – 2.57 (m, 3 H) 2.86 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.98 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.6 Hz, 1 H) 3.65 (s, 3 H) 4.11 - 4.23 (m, 2 H) 4.47 - 4.55 (m, 1 H) 6.23 (br d, J = 8.6 Hz, 1 H) 7.24 – 7.26 (m, 2 H) 7.31 - 7.35 (m, 1 H) 7.41 – 7.45 (m, 2 H) 7.51 – 7.59 (m, 4 H).

Example 3-13: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.29 (t, J = 7.2 Hz, 3 H) 1.36 – 1.51 (m, 4 H) 1.84 – 1.94 (m, 2 H) 1.98 – 2.06 (m, 3 H) 2.24 – 2.32 (m, 1H) 2.50 (A of ABX, J_{ab} = 16.2 Hz, J_{ax} = 5.3 Hz, 1 H) 2.53 (B of ABX, J_{ab} = 16.2 Hz, J_{bx} = 5.1 Hz, 1 H) 2.86 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.98 (B of ABX, J_{ab} = 13.6 Hz, Jbx = 6.6 Hz, 1 H) 3.66 (s, 3 H) 4.11 - 4.23 (m, 2 H) 4.46 - 4.55 (m, 1 H) 6.19 (br d, J = 8.8 Hz, 1 H) 7.24 – 7.26 (m, 2 H) 7.31 - 7.36 (m, 1 H) 7.41 – 7.45 (m, 2 H) 7.51 – 7.58 (m, 4 H).

Example 3-14: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.26 (t, J = 7.2 Hz, 3 H) 2.41 – 2.51 (m, 4 H) 2.62 – 2.66 (m, 2 H) 2.84 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.6 Hz, 1 H) 2.92 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.6 Hz, 1 H) 3.06 – 3.10 (m, 2 H) 4.08 - 4.19 (m, 2 H) 4.46 - 4.55 (m, 1 H) 6.78 (d, J = 8.9 Hz, 1 H) 7.10 – 7.12 (m, 1 H) 7.16 (d, J = 7.8 Hz, 1 H) 7.20 - 7.22 (m, 2 H) 7.29 - 7.31 (m, 1 H) 7.35 (t, J = 7.7 Hz, 1 H) 7.42 - 7.47 (m, 3 H) 7.54 – 7.59 (m, 2 H) 8.48 (d, J = 1.0 Hz, 1 H).

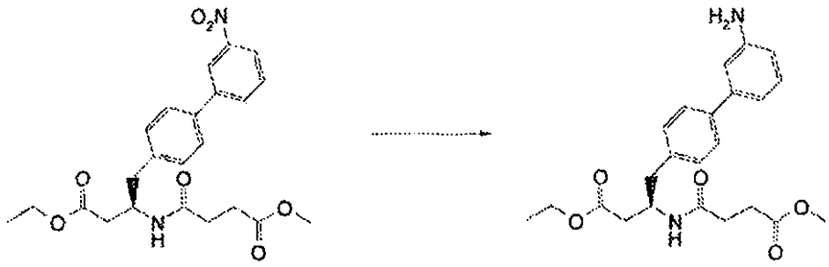
Example 3-16: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.24 (t, J = 7.1 Hz, 3 H) 2.38 – 2.42 (m, 2 H) 2.49 – 2.61 (m, 4 H) 2.82 – 3.00 (m, 2 H) 4.12 (q, J = 7.1 Hz, 2 H) 4.47 – 4.56 (m, 1 H) 5.12 (A of AB, J = 12.3 Hz, 1 H) 5.18 (B of AB, J = 12.3 Hz, 1 H) 6.26 (br d, J = 8.6 Hz, 1 H) 7.20 (d, J = 8.3 Hz, 2 H) 7.29 - 7.46 (m, 10 H) 7.54 – 7.54 (m, 1 H).

Example 3-17: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.23 (t, J = 7.2 Hz, 3 H) 1.86 – 1.92 (m, 2 H) 2.14 – 2.18 (m, 2 H) 2.24 – 2.28 (m, 2 H) 2.50 – 2.63 (m, 2 H) 2.82 – 2.99 (m, 2 H) 4.11 (q, J = 7.2 Hz, 2 H) 4.53 – 4.54 (m, 1 H) 5.12 (A of AB, J = 12.1 Hz, 1 H) 5.18 (B of AB, J = 12.1 Hz, 1 H) 6.12 – 6.14 (m, 1 H) 7.19 – 7.54 (m, 13 H).

Example 3-18: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.26 (t, J = 7.2 Hz, 3 H) 1.67 (s, 9 H) 2.46 – 2.57 (m, 2 H) 2.74 – 2.96 (m, 4 H) 3.41 – 3.45 (m, 2 H) 4.09 – 4.17 (m, 2 H) 4.50 – 4.59 (m, 1 H) 6.95 (br d, J = 8.6 Hz, 1 H) 7.18 (d, J = 8.1 Hz, 2 H) 7.27 – 7.42 (m, 7 H) 7.51 (t, J = 1.8 Hz, 1 H) 7.61 – 7.65 (m, 1 H) 7.86 – 7.93 (m, 1 H).

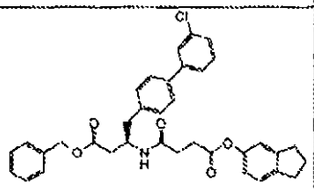
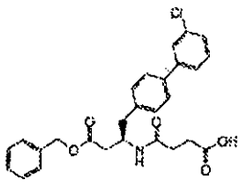
Example 3-19: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.28 (t, J = 7.2 Hz, 3 H) 1.43 (s, 9 H) 2.37 – 2.40 (m, 2 H) 2.50 – 2.59 (m, 4 H) 2.98 (d, J = 7.3 Hz, 2 H) 4.13 – 4.21 (m, 2 H) 4.48 – 4.56 (m, 1 H) 6.35 (br d, J = 8.8 Hz, 1 H) 7.22 – 7.44 (m, 6 H) 7.54 – 7.54 (m, 1 H).

Example 3-20: Synthesis of (R)-ethyl 4-(3'-aminobiphenyl-4-yl)-3-(4-methoxy-4-oxobutanamido)butanoate



A suspension of (R)-ethyl 3-(4-methoxy-4-oxobutanamido)-4-(3'-nitrobiphenyl-4-yl)butanoate (123 mg, 0.278 mmol) and Pd/C (59.2 mg, 0.028 mmol) in EtOH (2 ml) is allowed to stir under hydrogen at room temperature for 5.5 hours. The reaction mixture is filtered, and the solution is concentrated to give (R)-ethyl 4-(3'-aminobiphenyl-4-yl)-3-(4-methoxy-4-oxobutanamido)butanoate (105 mg); HPLC retention time = 0.84 minutes (condition B); MS (m+1) = 413.1; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, *J* = 7.2 Hz, 3 H) 2.41 – 2.65 (m, 6 H) 2.85 – 3.00 (m, 2 H) 3.67 (s, 3 H) 4.11 – 4.22 (m, 2 H) 4.46 – 4.54 (m, 1 H) 6.31 (br d, *J* = 8.8 Hz, 1 H) 6.71 – 6.74 (m, 1 H) 6.95 – 7.02 (m ,2 H) 7.21 – 7.25 (m, 3 H) 7.48 – 7.50 (m, 2 H).

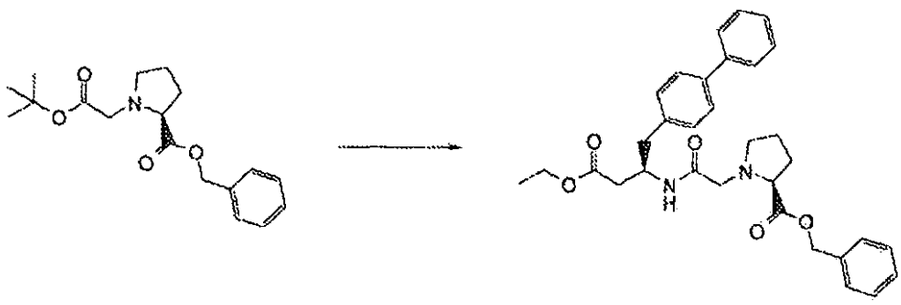
Following compounds are prepared using similar procedure as described in example 3-20:

Example #	Product	Condition	HPLC-RT (condition)	MS (M+1)
Example 3-22	 (R)-benzyl 4-(3'-chlorobiphenyl-4-yl)-3-(4-(2,3-dihydro-1H-inden-5-yloxy)-4-oxobutanamido)butanoate	 Example BB-13, PyBOP, indanol, DCM, RT	1.73 min. (B)	596.5

Example 3-22: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.03 – 2.11 (m, 2H) 2.48 – 2.62 (m, 4 H) 2.81 – 2.90 (m, 7 H) 2.95 – 3.00 (m, 1 H) 4.49 – 4.58 (m, 1 H) 5.07 – 5.18 (m,

2 H) 6.23 (br d, *J* = 8.6 Hz, 1 H) 6.79 – 6.82 (m, 1 H) 6.92 (s, 1 H) 7.15 – 7.20 (m, 3 H) 7.29 – 7.45 (m, 10 H) 7.52 – 7.53 (m, 1 H)

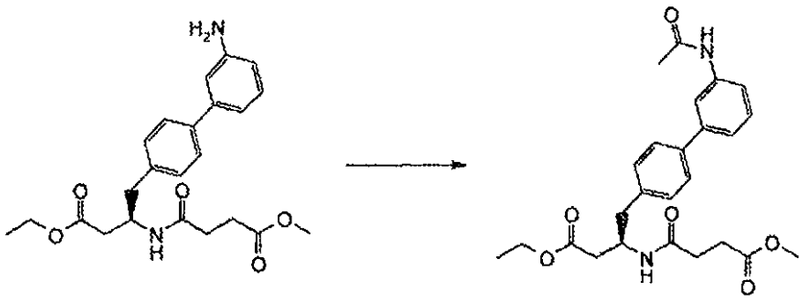
Example 3-23: Synthesis of (S)-benzyl 1-(2-((R)-1-(biphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-2-oxoethyl)pyrrolidine-2-carboxylate trifluoroacetic acid salt



To a solution of (*S*)-benzyl 1-(2-tert-butoxy-2-oxoethyl)pyrrolidine-2-carboxylate (200 mg, 0.626 mmol) and triethylsilane (0.250 ml, 1.565 mmol) in DCM (3 ml), TFA (0.965 ml, 12.52 mmol) is added at room temperature. After stirring for 24 hours, the reaction is concentrated to give crude.

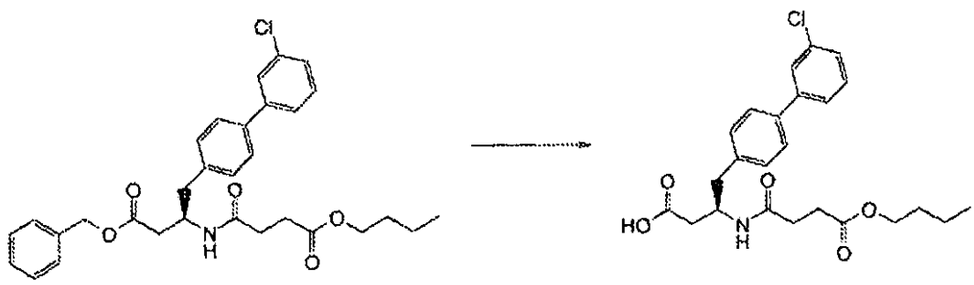
To a suspension of the crude, (*R*)-ethyl 3-amino-4-(biphenyl-4-yl)butanoate hydrochloride (266 mg, 0.832 mmol), WSC.HCl (0.180 g, 0.939 mmol) and HOAt (128 mg, 0.939 mmol) in DMF (4 ml), DIPEA (0.328 ml, 1.878 mmol) is added. After stirring for 4 hours, the reaction is diluted with H_2O and EtOAc. The products are extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude is subjected twice to column chromatography (heptane/EtOAc = 100:0 to0:100). Then, the obtained product is purified by preparative HPLC using a gradient of 20% MeCN/water (0.1 % TFA) to 100% MeCN to give (*S*)-benzyl 1-(2-((*R*)-1-(biphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-2-oxoethyl)pyrrolidine-2-carboxylate trifluoroacetic acid salt (28.5 mg) as a pale yellow solid; HPLC retention time = 1.84 minutes (condition D); MS (m+1) = 529.3; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.25 – 1.28 (m, 3 H) 1.74 – 1.85 (m, 2 H) 1.91 – 1.98 (m, 1 H) 2.09 – 2.19 (m, 1 H) 2.35 – 2.41 (m, 1 H) 2.46 (A of ABX, Jab = 15.7 Hz, Jax = 6.6 Hz, 1 H) 2.59 (B of ABX, J_{ab} = 13.7 Hz, J_{bx} = 5.7 Hz, 1 H) 2.78 – 2.83 (m, 1 H) 2.86 (A of ABX, J_{ab} = 13.8 Hz, J_{ax} = 8.1 Hz, 1 H) 2.99 (B of ABX, J_{ab} = 13.7 Hz, J_{bx} = 6.4 Hz, 1 H) 3.08 (A of AB, *J* = 16.5 Hz, 1 H) 3.35 (B of AB, *J* = 16.5 Hz, 1 H) 3.41 (dd, *J* = 9.1 and 5.1 Hz, 1 H) 4.11 – 4.20 (m, 2 H) 4.46 – 4.55 (m, 1 H) 5.10 (A of AB, *J* = 12.4 Hz, 1 H) 5.13 (B of AB, *J* = 12.4 Hz, 1 H) 7.26 – 7.27 (m, 2 H) 7.31 – 7.38 (m, 6 H) 7.40 – 7.44 (m, 2 H) 7.49 – 7.56 (m, 4 H) 7.74 (br d, *J* = 8.6 Hz, 1 H).

Example 3-24: Synthesis of (R)-ethyl 4-(3'-acetamidobiphenyl-4-yl)-3-(4-methoxy-4-oxobutanamido)butanoate



A solution of (R)-ethyl 4-(3'-aminobiphenyl-4-yl)-3-(4-methoxy-4-oxobutanamido)butanoate (70.5 mg, 0.171 mmol), Et_3N (0.027 ml, 0.205 mmol) and Ac_2O (0.019 ml, 0.205 mmol) in DCM (1.7 ml) is allowed to stir at room temperature for 65 hours. The reaction mixture is diluted with water. The products are extracted with DCM in a phase separator and concentrated to give crude (98 mg). The crude is purified by silica gel flash column chromatography (eluent: DCM/MeOH = 10:1) to give (R)-ethyl 4-(3'-acetamidobiphenyl-4-yl)-3-(4-methoxy-4-oxobutanamido)butanoate (71.5 mg); HPLC retention time = 1.45 minutes (condition D); MS (m+1) = 455.4; 1H NMR (400 MHz, CD3CN, mixture of rotamers, data for major rotamer) δ ppm 1.21 (t, *J* = 7.1 Hz, 3 H) 2.07 (s, 3 H) 2.31 – 2.34 (m, 2 H) 2.40 – 2.51 (m, 4 H) 2.82 – 2.84 (m, 2 H) 3.58 (s, 3 H) 4.07 (q, *J* = 7.1 Hz, 2 H) 4.34 – 4.43 (m, 1 H) 6.46 (br d, *J* = 8.9 Hz, 1 H) 7.28 – 7.39 (m, 4 H) 7.52 – 7.54 (m, 3 H) 7.80 (s, 1 H) 8.37 (br s, 1 H).

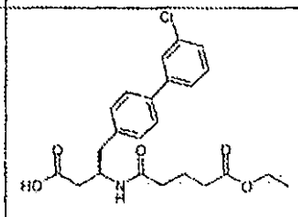
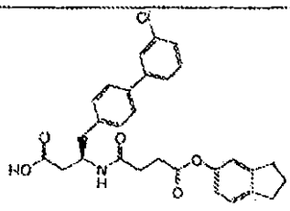
Example 3-25: Synthesis of (R)-3-(4-butoxy-4-oxobutanamido)-4-(3'-chlorobiphenyl-4-yl)butanoic acid

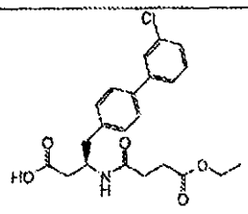


A suspension of (R)-benzyl 3-(4-butoxy-4-oxobutanamido)-4-(3'-chlorobiphenyl-4-yl)butanoate (178.9 mg, 0.334 mmol) and Pd/C (71.0 mg, 0.033 mmol) in EtOAc (3 ml) is

allowed to stir under hydrogen at room temperature for 1.5 hours. The reaction mixture is filtered, and concentrated to give crude. The resulting residue is purified by preparative HPLC using a gradient of 20% MeCN/water (0.1% TFA) to 100% MeCN to give (R)-3-(4-butoxy-4-oxobutanamido)-4-(3'-chlorobiphenyl-4-yl)butanoic acid (90.7 mg) as a white solid; HPLC retention time = 1.27 minutes (condition B); MS (m+1) = 446.24; 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.91 (t, J = 7.5 Hz, 3 H) 1.31 - 1.40 (m, 2 H) 1.55 - 1.62 (m , 2 H) 2.43 - 2.47 (m, 2 H) 2.52 - 2.69 (m , 4 H) 2.93 (A of ABX, J_{ab} = 13.7 Hz, J_{ax} = 7.7 Hz, 1 H) 3.00 (B of ABX, J_{ab} = 13.7 Hz, J_{bx} = 6.8 Hz, 1 H) 4.07 (t, J = 6.7 Hz, 2 H) 4.49 – 4.57 (m, 1 H) 6.31 (br d, J = 8.6 Hz, 1 H) 7.26 - 7.37 (m, 4 H) 7.43 - 7.46 (m, 1 H) 7.49 - 7.52 (m, 2 H) 7.55 (br t, J = 1.8 Hz, 1 H).
Chiral HPLC retention time = 4.33 min. Column: Daicel CHIRALPAK IA (4.6x100mm); flow rate = 1ml/min.; eluent: EtOH(containing 0.1% TFA)/heptane = 10/90 to 70/30 in 10min. (linear gradient).

Following compounds are prepared using similar procedure as described in example 3-24:

Example #	Product	Condition	HPLC-RT (condition)	MS (M+1)
Example 3-26	 (R)-4-(3'-chlorobiphenyl-4-yl)-3-(5-ethoxy-5-oxopentanamido)butanoic acid	Pd/C, H_2, EtOAc, RT	1.08 min. (B)	432.4
Example 3-27	 (R)-4-(3'-	Pd/C, H_2, EtOAc, acetone, RT	1.36 min. (B)	506.4

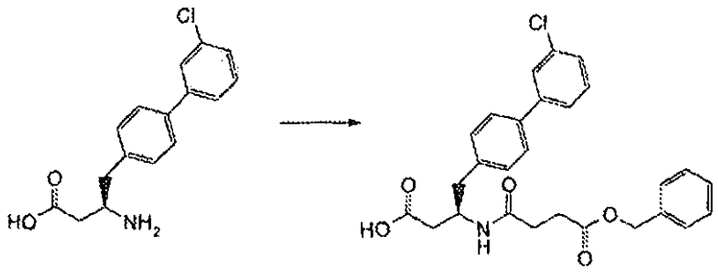
	chlorobiphenyl-4-yl)-3-(4-(2,3-dihydro-1H-inden-5-yloxy)-4-oxobutanamido)butanoic acid			
Example 3-28	 (R)-4-(3'-chlorobiphenyl-4-yl)-3-(4-ethoxy-4-oxobutanamido)butanoic acid	Pd/C, H_2, EtOAc, RT	1.00 min. (B)	418.4

Example 3-26: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.23 (t, J = 7.1 Hz, 3 H) 1.86 - 1.93 (m, 2 H) 2.57 (A of ABX, J_{ab} = 16.3 Hz, J_{ax} = 5.7 Hz, 1 H) 2.64 (B of ABX, J_{ab} = 16.3 Hz, J_{bx} = 5.2 Hz, 1 H) 2.94 (A of ABX, J_{ab} = 13.7 Hz, J_{ax} = 7.6 Hz, 1 H) 2.99 (B of ABX, J_{ab} = 13.7 Hz, J_{bx} = 7.2 Hz, 1 H) 4.10 (q, J = 7.1 Hz, 2 H) 4.51 – 4.60 (m, 1 H) 6.17 (br d, J = 8.6 Hz, 1 H) 7.26 - 7.37 (m, 4 H) 7.43 - 7.45 (m, 1 H) 7.49 - 7.52 (m, 2 H) 7.55 (br t, J = 1.8 Hz, 1 H).

Example 3-27: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.07 (quint, J = 7.4 Hz, 2 H) 2.51 - 2.63 (m, 4 H) 2.82 - 3.02 (m, 8 H) 4.50 – 4.59 (m, 1 H) 6.28 (d, J = 8.6 Hz, 1 H) 6.78 - 6.81 (m, 1 H) 6.91 (d, J = 1.8 Hz, 1 H) 7.26 - 7.36 (m, 6 H) 7.41 - 7.44 (m, 1 H) 7.47 - 7.50 (m, 2 H) 7.53 - 7.54 (m, 1 H).

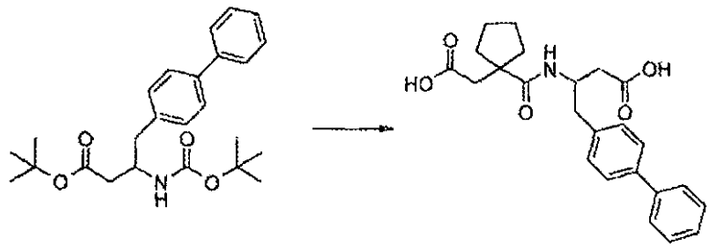
Example 3-28: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.24 (t, J = 7.2 Hz, 3 H) 2.44 - 2.69 (m , 6 H) 2.93 (A of ABX, J_{ab} = 13.7 Hz, J_{ax} = 7.8 Hz, 1 H) 3.00 (B of ABX, J_{ab} = 13.7 Hz, J_{bx} = 6.7 Hz, 1 H) 4.12 (q, J = 7.2 Hz, 2 H) 4.49 – 4.57 (m, 1 H) 6.35 (br d, J = 8.6 Hz, 1 H) 7.26 - 7.37 (m, 4 H) 7.43 - 7.46 (m, 1 H) 7.49 - 7.52 (m, 2 H) 7.55 (br t, J = 1.6 Hz, 1 H).

Example 3-29: Synthesis of (R)-3-(4-(benzyloxy)-4-oxobutanamido)-4-(3'-chlorobiphenyl-4-yl)butanoic acid



A solution of succinic acid mono-benzyl ester (71.1 mg, 0.342 mmol), EDCI (65.5 mg, 0.342 mmol) and HOAt (46.5 mg, 0.342 mmol) in DMF (1 ml), which is allowed to stir at room temperature for 1 hour, is added to a solution of (R)-3-amino-4-(3'-chlorobiphenyl-4-yl)butanoic acid (66 mg, 0.228 mmol) and DIPEA (0.080 ml, 0.456 mmol) in a mixed solvent DMF (2 ml) and water (2 ml). The reaction mixture is allowed to stir for 3 hours, and then diluted with H_2O. The products are extracted twice with EtOAc. The combined organic layer is washed with brine, dried over Na_2SO_4, filtered, and concentrated to give crude. The resulting residue is purified by preparative HPLC using a gradient of 20% MeCN/water (0.1% TFA) to 100% MeCN to give (*R*)-3-(4-(benzyloxy)-4-oxobutanamido)-4-(3'-chlorobiphenyl-4-yl)butanoic acid (42.4 mg) as a white solid; HPLC retention time = 1.22 minutes (condition B); MS (m+1) = 480.35; 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.44 - 2.75 (m, 6 H) 2.86 - 2.99 (m, 2 H) 4.48 - 4.56 (m, 1 H) 5.11 (s, 2 H) 6.29 (br d, *J* = 8.6 Hz, 1 H) 6.97 - 7.07 (m, 10 H) 7.25 - 7.36 (m, 2 H) 7.42 - 7.50 (m, 2 H) 7.54 (br t, *J* = 1.6 Hz, 1 H).

Example 3-30: Synthesis of 4-(biphenyl-4-yl)-3-(1-(carboxymethyl)cyclopentanecarboxamido)butanoic acid



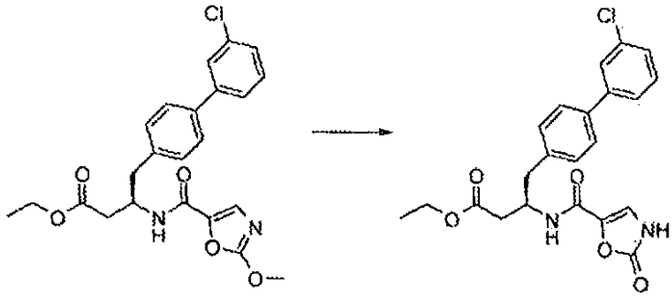
To tert-butyl 4-(biphenyl-4-yl)-3-(tert-butoxycarbonylamino)butanoate (110 mg, 0.267 mmol), a solution of 4 M HCl in 1,4-dioxane (0.668 ml, 2.67 mmol) is added. After stirring for 1 h, the reaction mixture is concentrated to give crude 3-amino-4-biphenyl-4-yl-butyric acid tert-butyl ester hydrochloride.

Next, to a solution of EDCI (51.2 mg, 0.267 mmol),1-hydroxy-7-azabenzotriazole (36.4 mg, 0.267 mmol) and 6 :1 mixture of 1-(2-(benzyloxy)-2-oxoethyl)cyclopentanecarboxylic acid and 2-(1-(benzyloxycarbonyl)cyclopentyl)acetic acid (65.6 mg, 0.214 mmol) in DMF (1 ml), which is stirred for 1.5 hours in advance, the crude 3-amino-4-biphenyl-4-yl-butyric acid tert-butyl ester hydrochloride and DIPEA (0.093 ml, 0.535 mmol) are added. After stirring for 2.5 hours, the reaction mixture is diluted with H2O, and the products are extracted with EtOAc. The organic layer is washed with brine, dried over Na2SO4, filtered, and concentrated. The obtained residue is purified by silica gel flash column chromatography (heptane/EtOAc = 100:0 to 0:100) to give crude tert-butyl 3-(1-(2-(benzyloxy)-2-oxoethyl)cyclopentanecarboxamido)-4-(biphenyl-4-yl)butanoate (38 mg).

Next, to the solution of the crude tert-butyl 3-(1-(2-(benzyloxy)-2-oxoethyl)cyclopentanecarboxamido)-4-(biphenyl-4-yl)butanoate (38 mg) in DCM (0.7 ml), TFA (0.263 ml, 3.42 mmol) is added. After stirring for 1 hour, the reaction mixture is concentrated to give crude 3-(1-(2-(benzyloxy)-2-oxoethyl)cyclopentanecarboxamido)-4-(biphenyl-4-yl)butanoic acid (39 mg).

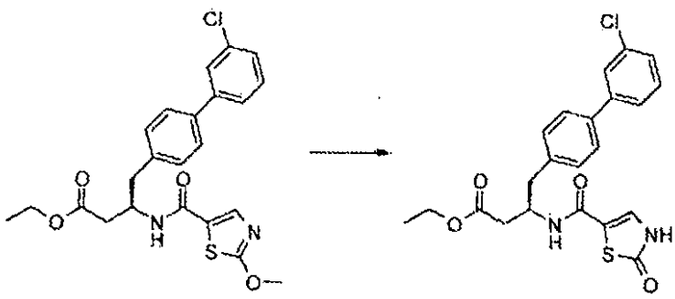
Next, A suspension of the crude (39 mg) and Pd/C (16.6 mg, 7.8 µmol) in EtOH (1 ml) is allowed to stir under hydrogen at room temperature for 4 hours. The reaction mixture is filtered, and concentrated to give crude. The resulting residue is purified by preparative HPLC using a gradient of 20% MeCN/water (0.1% TFA) to 100% MeCN to give 4-(biphenyl-4-yl)-3-(1-(carboxymethyl)cyclopentanecarboxamido)butanoic acid (12.7 mg); HPLC retention time = 1.16 minutes (condition B); MS (m+1) = 410.1; 1H NMR (400 MHz, DMSO-d6) δ ppm 1.39 - 1.53 (m, 6 H) 1.83 - 1.98 (m, 2 H) 2.34 - 2.45 (m, 2 H) 2.53 (s, 2 H) 2.73 - 2.86 (m, 2 H) 4.21 - 4.33 (m, 1 H) 7.27 (d, *J* = 8.1 Hz, 2 H) 7.32 - 7.37 (m, 2 H) 7.43 - 7.46 (m, 2 H) 7.55 - 7.58 (m, 2 H) 7.62 - 7.64 (m, 2 H) 7.84 (br d, *J* = 8.9 Hz, 1 H).

Example 3-31: Synthesis of (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-oxo-2,3-dihydrooxazole-5-carboxamido)butanoate



To a solution of (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-methoxyoxazole-5-carboxamido)butanoate, intermediate 14, (103 mg, 0.23 mmol) in dioxane (3 mL) is added 4 N solution of HCl in dioxane (0.29 mL, 1.16 mmol). The crude was stirred at room temperature for 2 hrs. The crude is concentrated and is diluted in water and EtOAc. The oganic layer is washed with brine, dried over $MgSO_4$, filtered, and concentrated. 50% of the crude is purified via RP-HPLC (SunFire C18, H_2O(0.1%TFA)/CH_3CN) to give (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-oxo-2,3-dihydrooxazole-5-carboxamido)butanoate (38 mg) as a white solid. HPLC retention time = 1.66 minutes (condition A); MS (m+1) = 429.4; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J*=7.1 Hz, 3 H) 2.51 - 2.69 (m, 2 H) 2.95 (dd, 1 H) 3.05 (dd, 1 H) 4.19 (q, 2 H) 4.58 - 4.75 (m, 1 H) 6.83 (d, *J*=8.8 Hz, 1 H) 7.26 - 7.33 (m, 4 H) 7.35 (t, *J*=7.7 Hz, 1 H) 7.45 (dt, *J*=7.6, 1.5 Hz, 1 H) 7.51 (d, *J*=8.3 Hz, 2 H) 7.56 (t, *J*=1.8 Hz, 1 H) 8.45 (br. s., 1 H)..

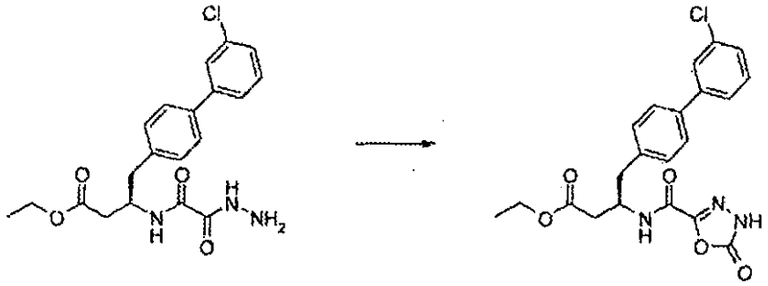
Example 3-32: Synthesis of (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-oxo-2,3-dihydrothiazole-5-carboxamido)butanoate



To a solution of (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-methoxythiazole-5-carboxamido)butanoate, intermediate 13, (170 mg, 0.37 mmol) in dioxane (5 mL) is added a solution of 4 M HCl in dioxane (0.5 mL, 2.00 mmol). The crude is stirred at room temperature for 3 hrs. The crude is concentrated. Part of the crude is purified via RP-HPLC

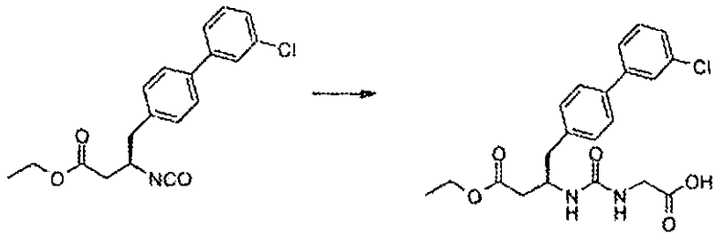
(SunFire C18, H_2O(0.1%TFA)/CH_3CN) to give (95 mg) of (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-oxo-2,3-dihydrothiazole-5-carboxamido)butanoate as a white solid. HPLC retention time = 1.82 minutes (condition D); MS (m+1) = 445.2. 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J*=7.1 Hz, 3 H) 2.46 - 2.70 (m, 2 H) 2.78-2.97 (m, 1 H) 3.07 (dd, *J*=13.0, 6.2 Hz, 1 H) 4.11 - 4.28 (m, 2 H) 4.51 - 4.69 (m, 1 H) 6.64 (d, *J*=8.1 Hz, 1H), 7.19-7.42 (m, 5 H) 7.44 (d, *J*=6.1 Hz, 1 H) 7.48-7.62 (m, 3H), 9.54 (br. s., 1 H).

Example 3-33: Synthesis of (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(5-oxo-4,5-dihydro-1,3,4-oxadiazole-2-carboxamido)butanoate



To a solution of (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-hydrazinyl-2-oxoacetamido)butanoate, intermediate 12, (289 mg, 0.72 mmol) in THF (8.5 mL) is added CDI (139 mg, 0.86 mmol) at room temperature. After stirring for 18 hour at room temperature, the reaction is quenched with H_2O and 1M HCl, and the crude is diluted with EtOAc. The organic layer is washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue is purified by RP-HPLC (SunFire C18, H_2O(0.1% TFA)/CH_3CN) and then lyophilized to give (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(5-oxo-4,5-dihydro-1,3,4-oxadiazole-2-carboxamido)butanoate (100 mg). HPLC retention time = 1.67 minutes (condition A); MS (m+1) = 430.2; 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.14 (t, *J*=7.1 Hz, 3 H) 2.52 - 2.70 (m, 2 H) 2.84 (dd, *J*=13.7, 8.4 Hz, 1 H) 2.90 (dd, *J*=13.7, 8.4 Hz, 1 H) 4.02 (q, *J*=7.1 Hz, 2 H) 4.42 - 4.58 (m, 1 H) 7.30 (d, *J*=8.1 Hz, 2 H) 7.37 - 7.43 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.57 - 7.66 (m, 3 H) 7.70 (t, *J*=1.9 Hz, 1 H) 8.98 (d, *J*=8.8 Hz, 1 H) 12.94 (s, 1 H).

Example 3-34: Synthesis of (R)-3-(3-Carboxymethyl-ureido)-4-(3'-chloro-biphenyl-4-yl)-butyric acid ethyl ester



To a solution of t-butyl 2-aminoacetate (19.08 mg, 0.145 mmol) and DIEA (18.8 mg, 0.145 mmol) in DMF (1 mL) is added Intermediate 45 (50 mg, 0.145 mmol) and the mixture is stirred at room temperature for 2 hours. The solvent is removed under reduced pressure to give (R)-3-(3-tert-butoxycarbonylmethyl-ureido)-4-(3'-chloro-biphenyl-4-yl)-butyric acid ethyl ester.

Next, to a solution of the above diester (70 mg, 0.147 mmol) in methylene chloride (2 mL) is added TFA (4 mL) and the mixture is stirred at room temperature for 18 hours. The solvents are removed under reduced pressure and the residue is purified by preparative HPLC using a gradient of 35% MeCN/water to 100% MeCN (+0.1% TFA). Lyophilization of the proper fractions gives the title compound; HPLC Retention time 1.42 minutes (condition C); MS 419.1 (M+1); 1H NMR (400 MHz, DMSO-d6): δ ppm 1.17 (t, J=7.07 Hz, 3H), 2.41 (d, J=7.07 Hz, 2H), 2.77-2.79 (m, 2H), 3.66-3.68 (m, 2H), 4.04 (q, J=7.07 Hz, 2H), 4.08-4.15 (m, 1H), 6.13 (t, J=5.81 Hz, 1H), 6.24 (d, J=8.59 Hz, 1H), 7.28-7.30 (m, 2H), 7.39-7.42 (m, 1H), 7.48 (t, J = 7.83 Hz, 1H), 7.62-7.64 (m, 3H), 7.71 (t, J=1.77 Hz, 1H), 12.42 (s, 1H).

Example 4-1: Synthesis of (R)-4-biphenyl-4-yl-3-(2-1H-tetrazol-5-yl-acetylamino)-butyric acid ethyl ester

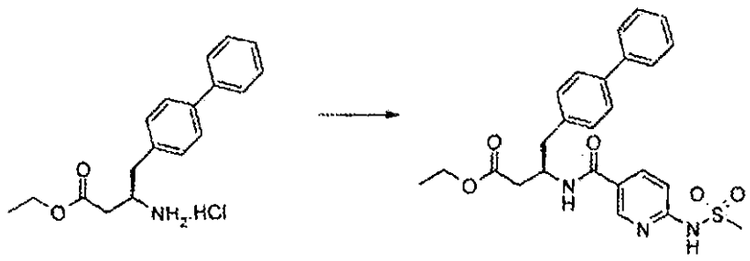


intermediate 2

To a solution of (R)-4-biphenyl-4-yl-3-tert-butoxycarbonylamino-butyric acid ethyl ester (100 mg, 0.261 mmol) in DCM (3 mL) at room temperature is added TFA (1 mL, 12.98 mmol) and the mixture is stirred at room temperature for 0.5 hour. The mixture is concentrated under reduced pressure to give (R)-3-amino-4-biphenyl-4-yl-butyric acid ethyl ester trifluoroacetic salt. HPLC retention time = 1.50 minutes (condition C); MS (m+1) = 384.

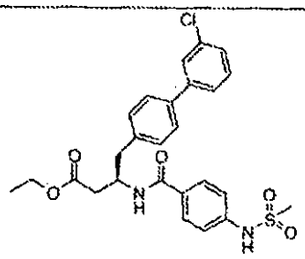
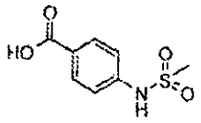
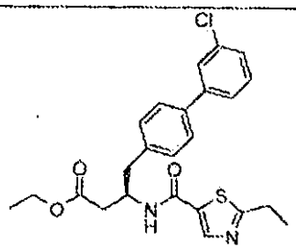
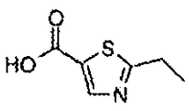
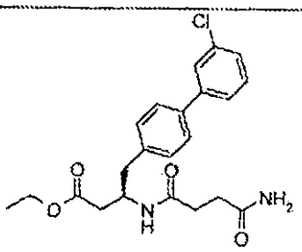
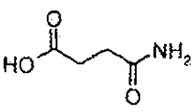
Next, to a suspension of (R)-3-amino-4-biphenyl-4-yl-butyric acid ethyl ester trifluoroacetic salt (0.074 g, 0.261 mmol) in DCM (10 mL) at room temperature is added 1H-tetrazole-5-acetic acid (0.050 g, 0.392 mmol). To the mixture at ice bath temperature is added bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.100 g, 0.392 mmol) and quickly followed by DIPEA (0.137 ml, 0.783 mmol). The reaction mixture is slowly warmed up to room temperature and stirred overnight. The reaction is extracted with DCM. The combined organic layer is washed with saturated $NaHCO_3$, saturated NH_4Cl, brine and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (R)-4-biphenyl-4-yl-3-(2-1H-tetrazol-5-yl-acetylamino)-butyric acid ethyl ester. HPLC retention time = 1.04 minutes (condition E); MS (m+1) = 394.

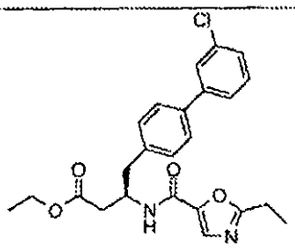
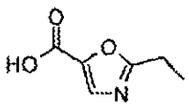
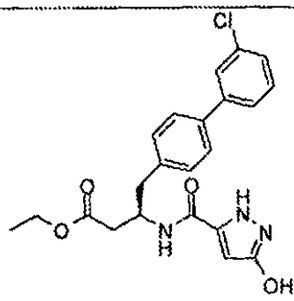
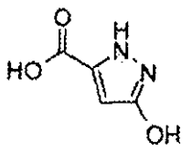
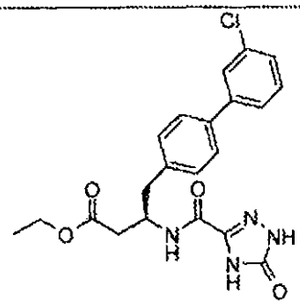
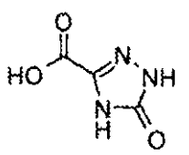
Example 4-2: Synthesis of (R)-ethyl 4-(biphenyl-4-yl)-3-(6-(methylsulfonamido)nicotinamido)butanoate

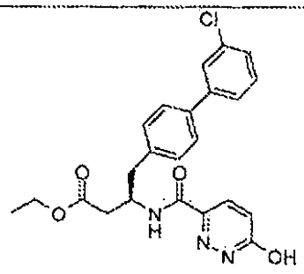
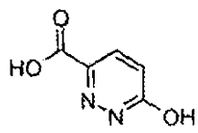
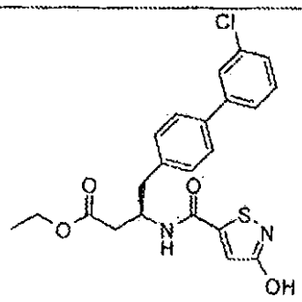
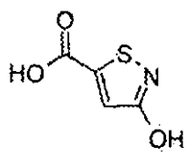
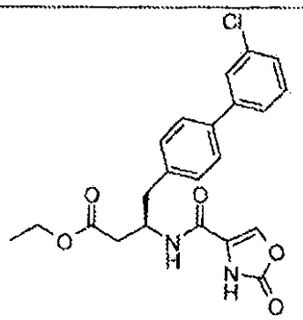
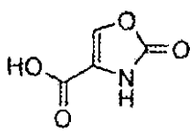


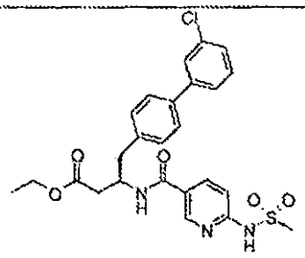
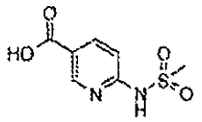
To a solution of (*R*)-ethyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride (103 mg, 0.32 mmol) and 6-(methylsulfonamido)nicotinic acid, intermediate 15, (84 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) and DMF (2 mL) is added TEA (0.18 mL, 1.29 mmol) and HATU (159 mg, 0.42 mmol) at room temperature. The crude is stirred at room temperature for 2 hrs. The crude is quenched with saturated $NaHCO_3$, diluted in EtOAc. The organic layer is washed with six times with water, brine, dried over $MgSO_4$, filtered, and concentrated. The crude is purified via RP-HPLC (SunFire C18, H_2O(0.1%TFA)/CH_3CN) to give (R)-ethyl 4-(biphenyl-4-yl)-3-(6-(methylsulfonamido)nicotinamido)butanoate as a white solid (4.1 mg). HPLC retention time = 1.61 minutes (condition A); MS (m+1) = 482.3. 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.22 (t, *J*=7.2 Hz, 3 H), 2.56 (t, *J*=4.8 Hz, 2 H), 2.84 - 2.92 (m, 1 H), 3.05 (dd, *J*=13.6, 6.1 Hz, 1 H), 3.16 (s, 3 H), 4.08 - 4.18 (m, 2 H), 4.57 - 4.71 (m, 1 H), 7.03 (d, *J*=8.3 Hz, 1 H), 7.10 (d, *J*=8.3 Hz, 1 H), 7.22 (d, *J*=8.3 Hz, 2 H), 7.26 - 7.31 (m, 1 H), 7.33 - 7.40 (m, 2 H), 7.44 - 7.54 (m, 5 H), 7.98 (dd, *J*=8.8, 2.3 Hz, 1 H), 8.52 (s, 1 H).

Following compounds are prepared using similar procedure as described in example 4-2:

Example #	Product	Reagent	LCMS-RT (condition)	MS (M+1)
Example 4-3	 (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(4-(methylsulfonamido)benzamido)butanoate	 EDCI and HOAt used instead of HATU	1.68 min (A)	515.2
Example 4-4	 (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-ethylthiazole-5-carboxamido)butanoate	 intermediate 26	1.63 min (A)	457.2
Example 4-5	 (R)-ethyl 3-(4-amino-4-oxobutanamido)-4-(3'-chlorobiphenyl-4-yl)butanoate	 EDCI and HOAt used instead of HATU	1.49 min (A)	417.3

Example 4-6	 (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-ethyloxazole-5-carboxamido)butanoate	 intermediate 23	1.60 min (A)	441.3
Example 4-7	 (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(3-hydroxy-1H-pyrazole-5-carboxamido)butanoate		1.82 min (A)	428.2
Example 4-8	 (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-carboxamido)butanoate	 EDCI and HOAt used instead of HATU	1.86 min (D)	429.2

Example 4-9	 (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(6-hydroxypyridazine-3-carboxamido)butanoate	 EDCI and HOAt used instead of HATU	1.82 min (D)	440.2
Example 4-10	 (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(3-hydroxyisothiazole-5-carboxamido)butanoate	 intermediate 20 EDCI and HOAt used instead of HATU	1.56 min (A)	445.3
Example 4-11	 (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-oxo-2,3-dihydrooxazole-4-carboxamido)butanoate	 Intermediate 19 EDCI and HOAt used instead of HATU	1.79 min (D)	429.1

Example 4-12	 (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(6-(methylsulfonamido)nicotinamido)butanoate	 intermediate 15	1.81 min. (D)	516.2

Example 4-3: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.1 Hz, 3 H) 2.52 - 2.67 (m, 2 H) 2.88 (dd, *J*=13.3, 8.0 Hz, 1 H) 2.95 (dd, *J*=13.3, 8.0 Hz, 1 H) 3.05 (s, 3 H) 4.02 (q, *J*=7.1 Hz, 2 H) 4.46 - 4.65 (m, 1 H) 7.23 (d, *J*=8.8 Hz, 2 H) 7.34 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.59 - 7.66 (m, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 7.75 (d, *J*=8.6 Hz, 2 H) 8.31 (d, *J*=8.3 Hz, 1 H) 10.07 (s, 1 H)

Example 4-4: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.1 Hz, 3 H) 1.28 (t, *J*=7.5 Hz, 3 H) 2.59 (d, *J*=7.1 Hz, 2 H) 2.81 - 2.94 (m, 2 H) 2.97 (q, *J*=7.6 Hz, 2 H) 4.03 (q, *J*=7.1 Hz, 2 H) 4.40 - 4.55 (m, 1 H) 7.32 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.58 - 7.65 (m, 3 H) 7.69 (t, *J*=1.9 Hz, 1 H) 8.18 (s, 1 H) 8.52 (d, *J*=8.3 Hz, 1 H)

Example 4-5: 1H NMR (400 MHz, CD_3OD) δ ppm 1.24 (t, *J*=7.1 Hz, 3 H) 2.38 - 2.60 (m, 6 H) 2.78 - 2.94 (m, 2 H) 4.10 (q, *J*=7.1 Hz, 2 H) 4.42 - 4.55 (m, 1 H) 7.32 (d, *J*=8.3 Hz, 2 H) 7.40 (t, *J*=7.83 Hz, 1 H) 7.50 - 7.53 (m, 4 H) 7.60 (t, *J*=1.89 Hz, 1 H)

Example 4-6: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.2 Hz, 3 H) 1.25 (t, *J*=7.6 Hz, 3 H) 2.53 - 2.65 (m, 2 H) 2.80 (q, *J*=7.6 Hz, 2 H) 2.84 - 2.96 (m, 2 H) 4.02 (q, *J*=7.1 Hz, 2 H) 4.42 - 4.60 (m, 1 H) 7.31 (d, *J*=8.3 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.59 (s, 1 H) 7.60 - 7.65 (m, 3 H) 7.69 (t, *J*=1.9 Hz, 1 H) 8.48 (d, *J*=8.6 Hz, 1 H)

Example 4-7: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.1 Hz, 3 H) 2.52 - 2.65 (m, 2 H) 2.85 (dd, *J*=13.6, 5.8 Hz, 1 H) 2.91 (dd, *J*=13.6, 5.8 Hz, 1 H) 4.02 (q, *J*=7.1 Hz, 2 H) 4.38

- 4.60 (m, 1 H) 5.89 (s, 1 H) 7.31 (d, *J*=8.3 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.58 - 7.65 (m, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 8.10 (d, *J*=8.6 Hz, 1 H)

Example 4-8: 1H NMR (400 MHz, CD_3OD) δ ppm 1.22 (t, *J*=7.2 Hz, 3 H) 2.56 - 2.72 (m, 2 H) 2.95 (d, *J*=7.3 Hz, 2 H) 4.11 (q, *J*=7.2 Hz, 2 H) 4.53 - 4.73 (m, 1 H) 7.28 - 7.36 (m, 3 H) 7.39 (t, *J*=7.8 Hz, 1 H) 7.48 - 7.55 (m, 3 H) 7.58 (t, *J*=1.8 Hz, 1 H)

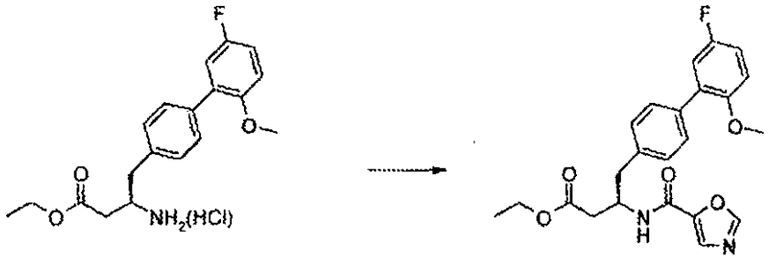
Example 4-9: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.1 Hz, 3 H) 2.53 - 2.71 (m, 2 H) 2.85 (dd, *J*=13.7, 8.3 Hz, 1 H) 2.96 (dd, *J*=13.7, 8.3 Hz, 1 H) 4.02 (q, *J*=7.1 Hz, 2 H) 4.45 - 4.63 (m, 1 H) 6.93 (dd, *J*=9.9, 2.3 Hz, 1 H) 7.30 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.42 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.61 (d, *J*=8.3 Hz, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 7.75 (d, *J*=9.9 Hz, 1 H) 8.45 (d, *J*=9.1 Hz, 1 H) 13.41 (d, *J*=2.0 Hz, 1 H)

Example 4-10: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.1 Hz, 3 H) 2.60 (d, *J*=7.6 Hz, 2 H) 2.90 (d, *J*=6.8 Hz, 2 H) 4.02 (q, *J*=7.2 Hz, 2 H) 4.39 - 4.53 (m, 1 H) 7.11 (s, 1 H) 7.32 (d, *J*=8.1 Hz, 2 H) 7.37 - 7.43 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.60 - 7.66 (m, 3 H) 7.70 (t, *J*=1.9 Hz, 1 H) 8.72 (d, *J*=8.3 Hz, 1 H) 11.76 (br. s., 1 H)

Example 4-11: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.27 (t, *J*=7.1 Hz, 3 H) 2.47 - 2.69 (m, 2 H) 2.90 (dd, *J*=13.6, 7.8 Hz, 1 H) 3.06 (dd, *J*=13.6, 6.6 Hz, 1 H) 3.06 (broad s, 1H) 4.07 - 4.28 (m, 2 H) 4.52 - 4.74 (m, 1 H) 7.21 - 7.37 (m, 5 H) 7.38 - 7.44 (m, 1 H) 7.48 (d, *J*=8.1 Hz, 2 H) 7.53 (t, *J*=1.6 Hz, 1 H) 9.50 (br. s., 1 H).

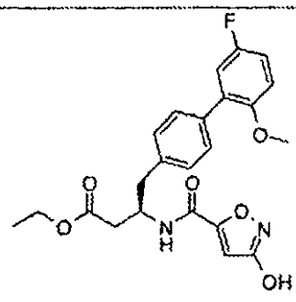
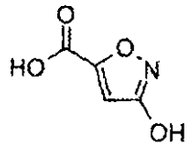
Example 4-12: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.1 Hz, 3 H) 2.59 (d, *J*=7.3 Hz, 2 H) 2.76 - 3.03 (m, 2 H) 4.03 (q, *J*=7.1 Hz, 2 H) 4.39 - 4.66 (m, 1 H) 7.02 (d, 1 H) 7.28 - 7.54 (m, 4 H) 7.54 - 7.80 (m, 4 H) 8.05 (dd, *J*=8.6, 2.3 Hz, 1 H) 8.45 (d, *J*=8.3 Hz, 1 H) 8.61 (br. s., 1 H).

Example 4-13: Synthesis of (R)-ethyl 4-(5'-fluoro-2'-methoxybiphenyl-4-yl)-3-(oxazole-5-carboxamido)butanoate



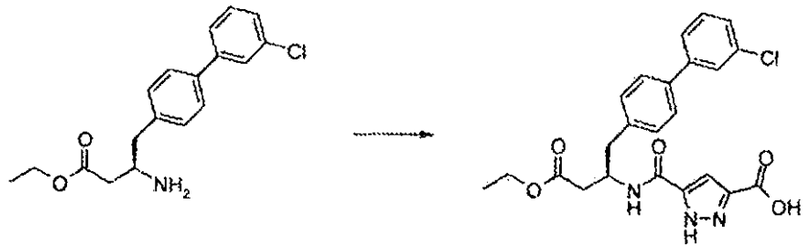
To a solution of oxazole-5-carboxylic acid (70 mg, 0.61 mmol) in DMF (1.5 mL) and DCM (1.5 mL) is added (R)-ethyl 3-amino-4-(5'-fluoro-2'-methoxybiphenyl-4-yl)butanoate hydrochloride, intermediate 10, (150 mg, 0.41 mmol), HATU (233 mg, 0.61 mmol), and TEA (284 µL, 2.04 mmol). After stirring for 2 hours, the reaction is quenched with H_2O, and the crude is diluted with EtOAc, the organic layer is washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue is purified by RP-HPLC (SunFire C18, H_2O(0.1% TFA)/CH_3CN), and then lyophilized to give (R)-ethyl 4-(5'-fluoro-2'-methoxybiphenyl-4-yl)-3-(oxazole-5-carboxamido)butanoate (157 mg). HPLC retention time = 1.50 minutes (condition A); MS (m+1) = 427.4; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.19 (t, *J*=7.2 Hz, 3 H) 2.46 - 2.62 (m, 2 H) 2.86 (dd, *J*=13.6, 8.1 Hz, 1 H) 3.02 (dd, *J*=13.6, 6.1 Hz, 1 H) 3.67 (s, 3 H) 4.05 - 4.15 (m, 2 H) 4.52 - 4.69 (m, 1 H) 6.76 - 6.82 (m, 1 H) 6.83 - 6.96 (m, 2 H) 7.11 - 7.21 (m, 3 H) 7.37 (d, *J*=8.1 Hz, 2 H) 7.61 (s, 1 H) 7.80 (s, 1 H)

Following compounds are prepared using similar procedure as described in example 4-13:

Example 4-14	 (R)-ethyl 4-(5'-fluoro-2'-methoxybiphenyl-4-yl)-3-(3-hydroxyisoxazole-5-carboxamido)butanoate		1.43 min. (A)	443.3

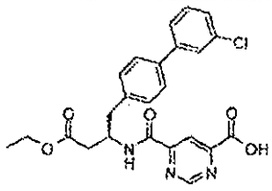
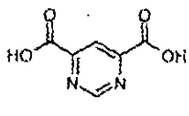
Example 4-14: 1H NMR (400 MHz, CD_3OD) δ ppm 1.21 (t, *J*=7.1 Hz, 3 H) 2.61 - 2.68 (m, 2 H) 2.95 (d, *J*=7.1 Hz, 2 H) 3.74 (s, 3 H) 4.10 (q, *J*=7.1 Hz, 2 H) 4.60 - 4.73 (m, 1 H) 6.43 (s, 1 H) 6.98 - 7.06 (m, 3 H) 7.27 (d, *J*=8.1 Hz, 2 H) 7.38 - 7.48 (m, 2 H) 8.78 (d, *J*=8.8 Hz, 1 H)

Example 4-15: Synthesis of 5-[(R)-1-(3'-Chloro-biphenyl-4-ylmethyl)-2-ethoxycarbonyl-ethylcarbamoyl]-1H-pyrazole-3-carboxylic acid



To a mixture of Intermediate 17-1 (130 mg, 0.367 mmol), 1H-pyrazole-3,5-dicarboxylic acid (74.5 mg, 0.477 mmol), EDCI (91 mg, 0.477 mmol) and HOBt (64.5 mg, 0.477 mmol) in DMF (3 mL) is added triethylamine (149 mg, 0.203 mmol) and the mixture is stirred at room temperature for 18 hours. Any insoluble material is removed by filtration and the filtrate is chromatographed by HPLC using a gradient of 10% MeCN/water to 100% MeCN (+0.1% TFA). Lyophilization of the proper fractions gives the title compound; HPLC Retention time 1.31 minutes (condition C); MS 456.2 (M+1); 1H NMR (400 MHz, DMSO-d6) δ ppm 1.12 (t, J=7.07 Hz, 3H), 2.54-2.67 (m, 2H), 2.84-2.97 (m, 2H), 4.02 (q, J=7.07 Hz, 2H), 4.54 (m, 1H), 7.11 (s, broad, 1H), 7.32 (d, J=8.08 Hz, 2H), 7.39 (m, 1H), 7.46 (t, 1H), 7.62 (d, J=8.08 Hz, 3H), 7.69 (s, 1H), 8.41 (s, broad, 1H).

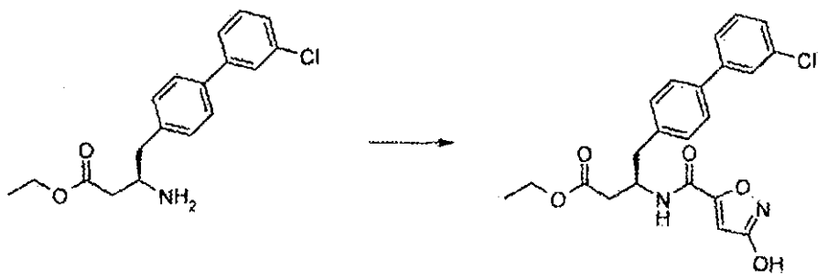
The following compounds are prepared using the procedure described for Example 4-15.

Example #	Product	Reagent	HPLC-RT (condition)	MS (M+1)
Example 4-16	 6-[(R)-1-(3'-Chloro-		1.31 min. (C)	468.2

	biphenyl-4-ylmethyl)-2-ethoxycarbonyl-ethylcarbamoyl]-pyrimidine-4-carboxylic acid			

Example 4-16: 1H NMR (400 MHz, DMSO-d6): δ ppm 1.11 (t, J=7.07 Hz, 3H), 2.59-2.79 (m, 2H), 2.87-2.92 (m, 1H), 2.98-3.04 (m, 1H), 4.01 (q, J=7.33 Hz, 2H), 4.57-4.66 (m, 1H), 7.30-7.32 (m, 2H), 7.37-7.40 (m,1H), 7.45 (t, J=7.58 Hz, 1H), 7.59-7.61 (m, 3H), 7.68 (t, J=1.77 Hz, 1H), 8.16 (s, 1H), 9.10 (d, J=9.35 Hz, 1H), 9.31 (s, 1H).

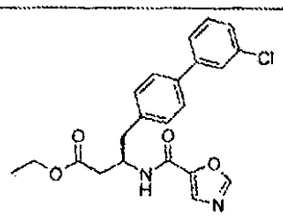
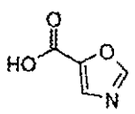
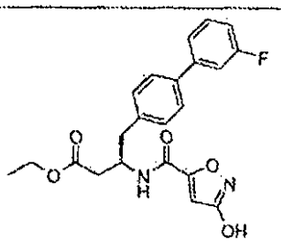
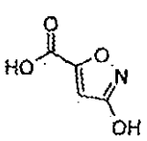
Example 4-17: (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(3-hydroxy-isoxazole-5-carbonyl)-amino]-butyric acid ethyl ester



To a solution of intermediate 16-1 (40.6 mg, 0.315 mmol) and HATU (144 mg, 0.378 mmol) in DMF (2 mL) is added pyridine (74.7 mg, 0.76 mL, 0.944 mmol) and the mixture is stirred at room temperature for 15 minutes. Then Intermediate 17-1 is added and stirring is continued for 2 hours. Any insoluble is removed by filtration and the filtrate is chromatographed by HPLC using a gradient of 10% MeCN/water to 100% MeCN (+0.1% TFA). Lyophilization of the proper fractions gives the title compound. HPLC Retention time 1.36 minutes (condition C); MS 429.1 (M+1); 1H NMR (400 MHz, DMSO-d6) δ ppm 1.13 (t, J=7.07 Hz, 3 H) 2.60 (dd, J=6.95, 3.66 Hz, 2 H) 2.81 - 2.95 (m, 2 H) 4.02 (q, J=7.24 Hz, 2 H) 4.49 (d, J=7.83 Hz, 1 H) 6.49 (s, 1 H) 7.31 (d, J=8.34 Hz, 2 H) 7.37 - 7.43 (m, 1 H) 7.47 (t, J=7.83 Hz, 1 H) 7.59 - 7.66 (m, 3 H) 7.70 (t, J=1.89 Hz, 1 H) 8.83 (d, J=8.84 Hz, 1 H).

The following compounds are prepared using the procedure described for Example 4-17

Example #	Product	Reagent	HPLC-RT	MS

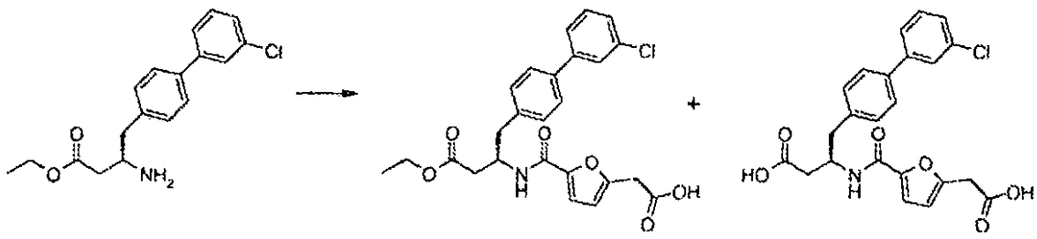
			(condition)	(M+1)
Example 4-18	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(oxazole-5-carbonyl)-amino]-butyric acid ethyl ester		1.48 min. (C)	413.1
Example 4-19	 (R)-4-(3'-Fluoro-biphenyl-4-yl)-3-[(3-hydroxy-isoxazole-5-carbonyl)-amino]-butyric acid ethyl ester		1.22 min. (C)	413.1

Example 4-18: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.12 (t, J=7.07 Hz, 3 H) 2.60 (dd, J=6.95, 2.65 Hz, 2 H) 2.82 - 2.96 (m, 2 H) 4.02 (q, J=7.07 Hz, 2 H) 4.45 - 4.58 (m, 1 H) 7.31 (d, J=8.34 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 (t, J=7.83 Hz, 1 H) 7.58 - 7.65 (m, 3 H) 7.69 (t, J=1.77 Hz, 1 H) 7.72 (s, 1 H) 8.55 (s, 1 H) 8.63 (d, J=8.59 Hz, 1 H).

Example 4-19: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.07 Hz, 3 H) 2.54 - 2.75 (m, 2 H) 2.76 - 3.02 (m, 2 H) 4.02 (q, *J*=7.07 Hz, 2 H) 4.29 - 4.70 (m, 1 H) 6.49 (s, 1 H) 6.96 - 7.23 (m, 1 H) 7.30 (d, *J*=8.08 Hz, 2 H) 7.44 - 7.58 (m, 3 H) 7.64 (d, *J*=8.08 Hz, 2 H) 8.83 (d, *J*=8.59 Hz, 1 H) 11.68 (s, 1 H).

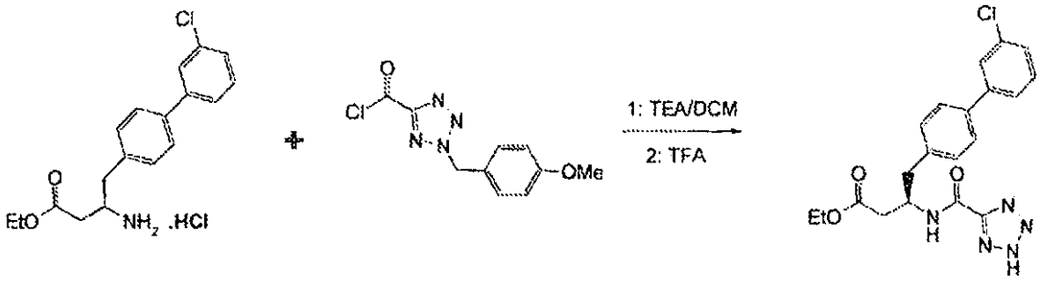
Example 4-20: (R)-3-[(5-Carboxymethyl-furan-2-carbonyl)-amino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid ethyl ester and

Example 4-21: (R)-3-[(5-Carboxymethyl-furan-2-carbonyl)-amino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid



The reaction is performed similar to Example 4-15 using Intermediate 16-1 and Intermediate 44 to give (R)-4-(3'-chloro-biphenyl-4-yl)-3-[(5-methoxycarbonylmethyl-furan-2-carbonyl)-amino]-butyric acid ethyl ester. HPLC Retention time 1.38 minutes (condition C).
Next, to a solution of the above diester (235 mg, 0.486 mmol) in EtOH (5 mL) is added 1N NaoH (0.486 mL) and the mixture is stirred at room temperature for 4 hours. The solvent is removed under reduced pressure and water (4 mL) is added. The solution is acidified with 1N HCl and the mixture is extracted with EtOAc. The organic phase is dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is purified by preparative HPLC using a gradient of 10% MeCN/water to 100% MeCN (+0.1% TFA). Lyophilization of the proper fractions gives the title compounds. (R)-3-[(5-Carboxymethyl-furan-2-carbonyl)-amino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid ethyl ester. HPLC Retention time 1.35 minutes (condition C); MS 470.0 (M+1); 1H NMR (400 MHz, DMSO-d6) δ ppm 1.13 (t, J= 7.07 Hz, 3H), 2.50-2.64 (m, 2H), 2.81-2.95 (m, 2H), 3.74 (s, 2H), 4.01 (q, J=7.07 Hz, 2H), 4.51 (m, 1H), 6.99 (d, J=3.28 Hz, 1H), 7.31 (d, J=8.34 Hz, 2H), 7.38-7.41 (m, 1H), 7.47 (t, 1H), 7.62 (d, J=8.08 Hz, 3H), 7.69 (t, 1H), 8.24 (d, J=8.84 Hz, 1H).
(R)-3-[(5-Carboxymethyl-furan-2-carbonyl)-amino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid. HPLC Retention time 0.94 minutes (condition C); MS 442.0 (M+1); 1H NMR (400 MHz, DMSO-d6) δ ppm 2.44-2.58 (m, 2H), 2.81-2.94 (m, 2H), 3.74 (s, 2H), 4.48 (m, 1H), 6.39 (d, J=3.28 Hz, 1H),6.99 (d, J=3.54 Hz, 1H), 7.30 (d, J=8.34 Hz, 2H), 7.38-7.41 (m, 1H), 7.47 (t, 1H), 7.62 (d, J=8.34 Hz, 3H), 7.70 (t, J=1.77 Hz,1H), 8.22 (d, J=8.84 Hz, 1H).

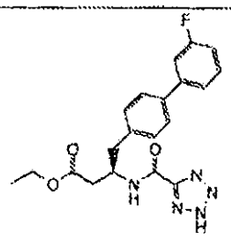
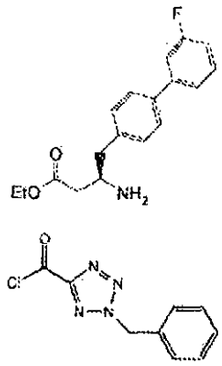
Example 4-22: (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(2H-tetrazole-5-carbonyl)-amino]-butyric acid ethyl ester

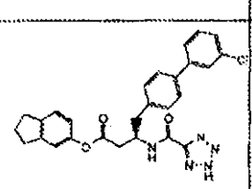
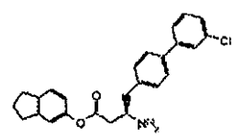
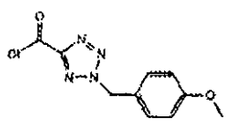


To a solution of intermediate 16-1 in DCM (8 ml) at room temperature is added 2-(4-methoxy-benzyl)-2H-tetrazole-5-carbonyl chloride and followed by TEA (0.293 ml, 2.100 mmol). The reaction is stirred at room temperature for 5 min. The reaction is quenched by brine and is extracted with DCM. The combined organic layer is washed with brine and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography (15% to 40% EtOAc/Heptane). The obtained residue in TFA (5 ml, 64.9 mmol) is heated at 80 °C for 0.5 hours. The reaction is concentrated under reduced pressure to give (R)-4-(3'-chloro-biphenyl-4-yl)-3-[(2H-tetrazole-5-carbonyl)-amino]-butyric acid ethyl ester.

HPLC retention time = 1.31 minutes (condition B); MS (m+1) = 414.1; 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.11 (t, J=7.1 Hz, 3 H), 2.63 (dd, J=15.4, 5.6 Hz, 1 H), 2.72 (dd, J=15.4, 8.3 Hz, 1 H), 2.86 - 2.99 (m, 2 H), 4.02 (q, J=7.1 Hz, 2 H), 4.55 - 4.67 (m, 1 H), 7.32 (d, J=8.1 Hz, 2 H), 7.37 - 7.42 (m, 1 H), 7.46 (t, J=7.8 Hz, 1 H), 7.60 (d, J=8.1 Hz, 3 H), 7.68 (t, J=1.8 Hz, 1 H), 9.37 (d, J=8.8 Hz, 1 H).

Following compounds are prepared using similar procedure as described in example 4-22:

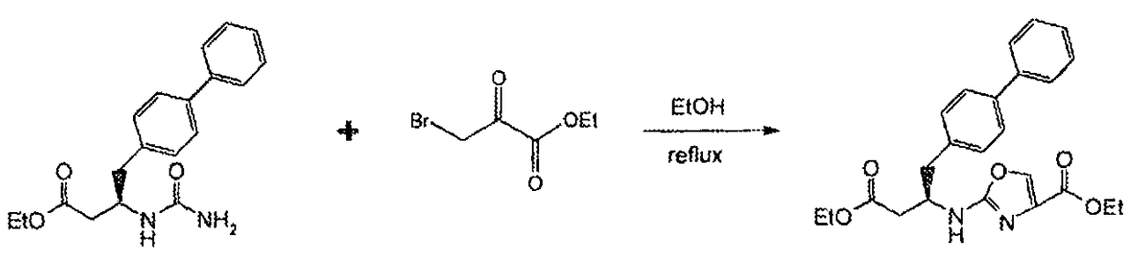
Example #	Product	Starting Material	Deprotection Condition	HPLC-RT (condition)	MS (M+1)
Example 4-23	 (R)-4-(3'-Fluoro-biphenyl-4-yl)-3-[(2H-tetrazole-5-carbonyl)-amino]-		1 atm. H_2, 10% Pd/C, EtOH, RT	1.12 min. (B)	398.2

	butyric acid ethyl ester				
Example 4-24	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(2H-tetrazole-5-carbonyl)-amino]-butyric acid indan-5-yl ester	 	TFA, 80 °C	1.68 min. (B)	502.3

Example 4-23: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, J=7.2 Hz, 3 H), 2.59 - 2.67 (m, J=15.4, 5.6 Hz, 1 H), 2.72 (dd, J=15.4, 8.3 Hz, 1 H), 2.85 - 3.01 (m, 2 H), 4.02 (q, J=7.1 Hz, 2 H), 4.55 - 4.67 (m, 1 H), 7.11 - 7.19 (m, 1 H), 7.32 (d, J=8.3 Hz, 2 H), 7.42 - 7.51 (m, 3 H), 7.61 (d, J=8.3 Hz, 2 H), 9.34 (d, J=8.8 Hz, 1 H).

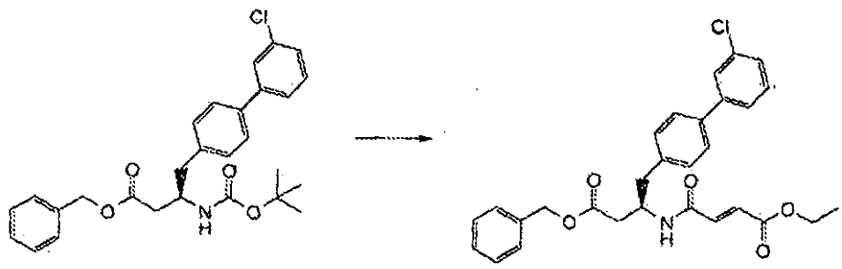
Example 4-24: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.95 - 2.06 (m, 2 H), 2.75 - 2.92 (m, 6 H), 2.95 (dd, J=13.5, 5.9 Hz, 1 H), 3.06 (dd, J=13.6, 8.1 Hz, 1 H), 4.64 - 4.76 (m, 1 H), 6.78 (dd, J=8.1, 2.3 Hz, 1 H), 6.88 (d, J=1.5 Hz, 1 H), 7.17 (d, J=8.1 Hz, 1 H), 7.34 - 7.41 (m, 3 H), 7.46 (t, J=7.8 Hz, 1 H), 7.59 - 7.65 (m, 3 H), 7.70 (t, J=1.8 Hz, 1 H), 8.43 (d, J=8.8 Hz, 1 H).

Example 4-25: 2-((R)-1-Biphenyl-4-ylmethyl-2-ethoxycarbonyl-ethylamino)-oxazole-4-carboxylic acid ethyl ester



To a suspension of (R)-4-biphenyl-4-yl-3-ureido-butyric acid ethyl ester (169 mg, 0.518 mmol) in EtOH (5 ml) at ice bath is added ethyl bromopyruvate (0.098 ml, 0.777 mmol). The reaction is warmed up slowly to room temperature and stirred at reflux overnight. The reaction is concentrated and the residue is taken up in EtOAc and H_2O. The combined organic layer is washed with brine and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2-((R)-1-biphenyl-4-ylmethyl-2-ethoxycarbonyl-ethylamino)-oxazole-4-carboxylic acid ethyl ester. HPLC retention time = 1.42 minutes (condition B); MS (m+1) = 423.

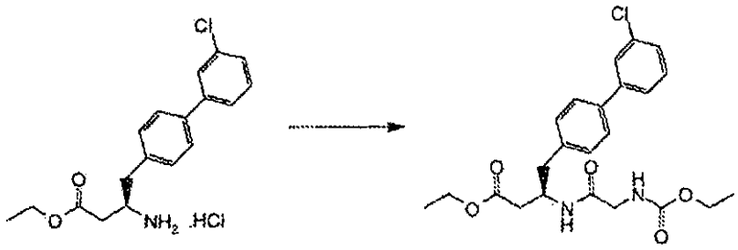
Example 4-26: Synthesis of (*R,E*)-ethyl 4-(4-(benzyloxy)-1-(3'-chlorobiphenyl-4-yl)-4-oxobutan-2-ylamino)-4-oxobut-2-enoate



To (*R*)-benzyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate (87.6 mg, 0.183 mmol) is added a solution of HCl in 1,4-dioxane (0.456 mL, 1.825 mmol) at room temperature. After stirring for 3 hours, the reaction mixture is concentrated under reduced pressure to give (*R*)-benzyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride. A mixture of (R)-benzyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride, fumaric acid monoethyl ester (33.4 mg, 0.220 mmol), EDCI (63.3 mg, 0.330 mmol), DIPEA (0.058 ml, 0.330 mmol) and HOAt (44.9 mg, 0.330 mmol) in DMF (1.8 ml) is allowed to stir at room temperature for 3 hour. The reaction mixture is diluted with water, and then the products are extracted wtih EtOAc. The organic layer is washed with NH4OH, 1M HClaq and brine, dried over Na2SO4, filtered, and concentrated to give crude. The obtained residue is purified by silica gel flash column chromatography (heptane/EtOAc = 100:0 to 0:100) to give (*R,E*)-ethyl 4-(4-(benzyloxy)-1-(3'-chlorobiphenyl-4-yl)-4-oxobutan-2-ylamino)-4-oxobut-2-enoate (72.9 mg); HPLC retention time = 1.40 minutes (condition B); MS (m+1) = 506.3; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.31 (t, *J* = 7.1 Hz, 3 H) 2.58 (A of ABX, J_{ab} = 16.4 Hz, J_{ax} = 5.3 Hz, 1 H) 2.6 (B of ABX, J_{ab} = 16.4 Hz, J_{bx} = 5.1 Hz, 1 H) 2.88 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.1 Hz, 1 H) 3.03

(B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.3 Hz, 1 H) 4.24 (q, J = 7.1 Hz, 2 H) 4.56 – 4.64 (m, 1 H) 5.12 (A of AB, J = 12.1 Hz, 1 H) 5.18 (B of AB, J = 12.1 Hz, 1 H) 6.57 (br d, J = 9.1 Hz, 1 H) 6.77 (A of AB, J = 15.4 Hz, 1 H) 6.81 (B of AB, J = 15.4 Hz, 1 H) 7.19 (br d, J = 8.1 Hz, 2 H) 7.29 – 7.47 (m, 10 H) 7.53 – 7.54 (m, 1 H).

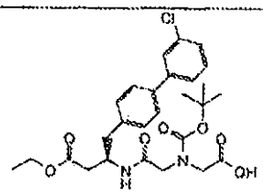
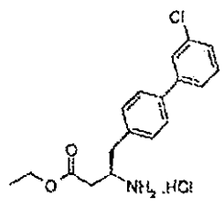
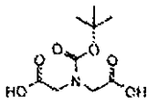
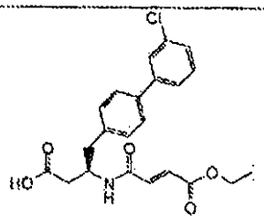
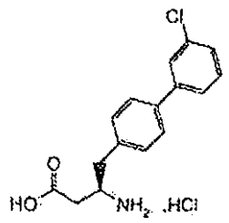
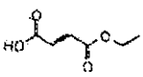
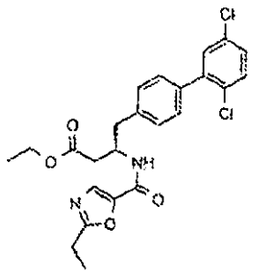
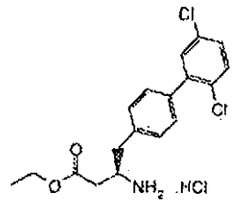
Example 4-27: Synthesis of (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-(ethoxycarbonylamino)acetamido)butanoate

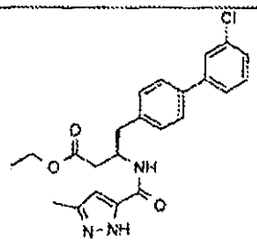
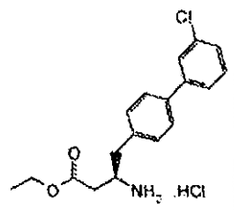
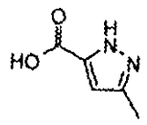
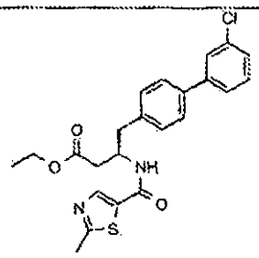
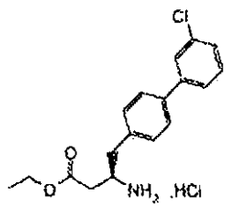
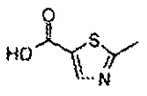
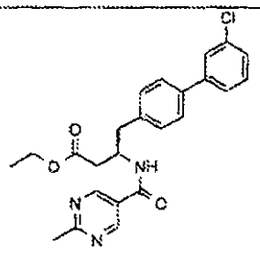
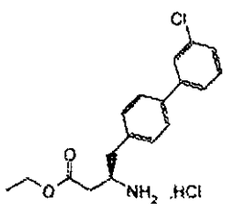
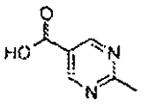


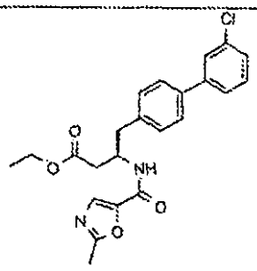
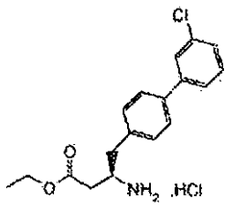
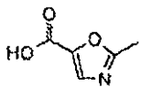
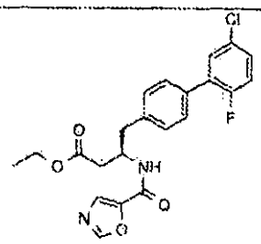
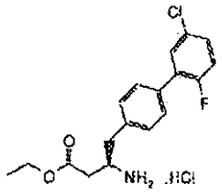
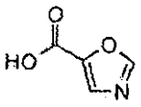
A mixture of (*R*)-ethyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride (173 mg, 0.488 mmol), 2-(ethoxycarbonylamino)acetic acid (86 mg, 0.488 mmol), EDCI (140 mg, 0.732 mmol), DIPEA (0.128 ml, 0.732 mmol) and HOAt (100 mg, 0.732 mmol) in DMF (2.5 ml) is allowed to stir at room temperature for 1 hour. The reaction mixture is diluted with water, and then the precipitated solid is collected on a funnel, washed with H2O, and dried under reduced pressure to give crude. The obtained residue is purified by silica gel flash column chromatography (heptane/EtOAc = 100:0 to 0:100) to give (*R*)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-(ethoxycarbonylamino)acetamido)butanoate (161 mg); HPLC retention time = 1.16 minutes (condition B); MS (m+1) = 447.3; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.25 (t, J = 7.07 Hz, 3 H) 1.29 (t, J = 7.07 Hz, 3 H) 2.50 (A of ABX, J_{ab} = 16.2 Hz, J_{ax} = 5.3 Hz, 1 H) 2.54 (B of ABX, J_{ab} = 16.2 Hz, J_{bx} = 5.3 Hz, 1 H) 2.89 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.99 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.6 Hz, 1 H) 3.80 (be d, J = 5.8 Hz, 2 H) 4.12 – 4.23 (m , 4 H) 4.48 – 4.56 (m, 1 H) 5.15 (br s, 1 H) 6.64 (br d, J = 8.8 Hz, 1 H) 7.25 – 7 .27 (m, 2 H) 7.29 – 7.38 (m, 2 H) 7.43 – 7.46 (m, 1 H) 7.49 – 7.52 (m, 2 H) 7.55 – 7.56 (m, 1 H).

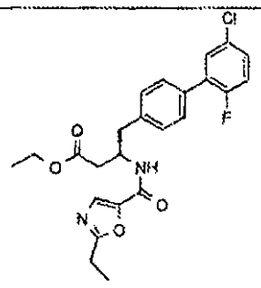
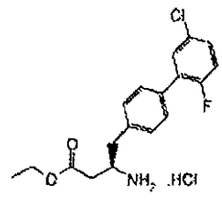
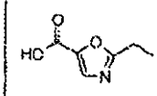
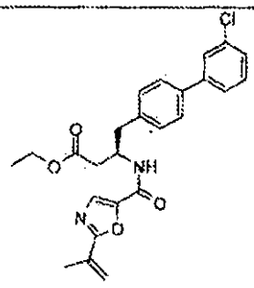
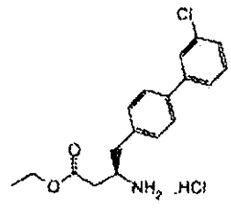
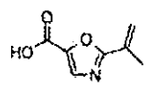
Following compounds are prepared using similar procedure as described in example 4-27:

Example #	Product	Starting Material	Condition	HPLC-RT (condition)	MS (M+1)

Example 4-28	 (R)-2-(tert-butoxycarbonyl(2-(1-(3'-chlorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-2-oxoethyl)amino)acetic acid		 EDCI, HOAT, DIPEA, DMF, rt	1.53 min. (A)	533.2
Example 4-29	 (*R,E*)-4-(3'-chlorobiphenyl-4-yl)-3-(4-ethoxy-4-oxobut-2-enamido)butanoic acid		 EDCI, HOAT, DIPEA, DMF, rt	1.00 min. (B)	416.1
Example 4-30	 (R)-4-(2',5'-dichloro-biphenyl-4-yl)-3-[(2-ethyl-oxazole-5-carbonyl)-amino]-		 HATU, TEA, DMF/DCM, rt	1.64 min. (A)	476.2

	butyric acid ethyl ester				
Example 4-31	 (R)-4-(3'-chloro-biphenyl-4-yl)-3-[(5-methyl-2H-pyrazole-3-carbonyl)-amino]-butyric acid ethyl ester		 HATU, TEA, DMF/DCM, rt	1.66 min. (A)	426.1
Example 4-32	 (R)-4-(3'-chloro-biphenyl-4-yl)-3-[(2-methyl-thiazole-5-carbonyl)-amino]-butyric acid ethyl ester		 HATU, TEA, DMF/DCM, rt	1.69 min. (A)	443.2
Example 4-33			 HATU,	1.66 min. (A)	438.2

	(R)-4-(3'-chloro-biphenyl-4-yl)-3-[(2-methyl-pyrimidine-5-carbonyl)-amino]-butyric acid ethyl ester		TEA, DMF/DCM, rt		
Example 4-34	 (R)-4-(3'-chloro-biphenyl-4-yl)-3-[(2-methyl-oxazole-5-carbonyl)-amino]-butyric acid ethyl ester		 HATU, TEA, DMF/DCM, rt	1.71 min. (A)	427.1
Example 4-35	 (R)-4-(5'-chloro-2'-fluoro-biphenyl-4-yl)-3-[(oxazole-5-carbonyl)-amino]-butyric acid ethyl ester		 HATU, TEA, DMF/DCM, rt	1.75 min. (A)	431.1

Example 4-36	 (R)-4-(5'-chloro-2'-fluoro-biphenyl-4-yl)-3-[(2-ethyl-oxazole-5-carbonyl)-amino]-butyric acid ethyl ester		 HATU, TEA, DMF/DCM, rt	1.81 min. (A)	459.1
Example 4-37	 (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-(prop-1-en-2-yl)oxazole-5-carboxamido)butanoate		 HATU, TEA, DMF/DCM, rt	1.86 min. (A)	453.2

Example 4-29: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.31 (t, J = 7.2 Hz, 3 H) 2.64 (A of ABX, J_{ab} = 16.8 Hz, J_{ax} = 5.1 HZ, 1 H) 2.68 (B of ABX, J_{ab} = 16.8 Hz, J_{bx} = 5.1 Hz, 1 H) 2.97 (A of ABX, J_{ab} = 13.7 Hz, J_{ax} = 8.1 HZ, 1 H) 3.08 (B of ABX, J_{ab} = 13.7 Hz, J_{bx} = 6.7 Hz, 1 H) 4.25 (q, J = 7.2 Hz, 2 H) 4.58 – 4.67 (m, 1 H) 6.66 (d, J = 8.8 Hz, 1 H) 6.80 (A of AB, J = 15.4 Hz, 1 H) 6.97 (B of AB, J = 15.4 Hz, 1 H) 7.27 – 7.37 (m, 4 H) 7.43 – 7.45 (m, 1 H) 7.51 (d, J = 8.3 Hz, 2 H) 7.55 – 7.56 (m, 1 H).

Example 4-30: 1H NMR (400 MHz, CD3OD) δ ppm 1.21 (t, J=7.2 Hz, 3 H) 1.34 (t, J=7.6 Hz, 3 H) 2.68 (d, J=6.8 Hz, 2 H) 2.84 - 2.87 (m, 2 H) 2.98 - 3.00 (m, 2 H) 4.10 (q, J=7.1 Hz, 2 H) 4.66 - 4.78 (m, 1 H) 7.27 - 7.37 (m, 6 H) 7.41 - 7.47 (m, 1 H) 7.54 (s, 1 H).

Example 4-31: 1H NMR (400 MHz, CD3OD) δ ppm 1.20 (t, J=7.1 Hz, 3 H) 2.28 (s, 3 H) 2.62 (d, J=7.1 Hz, 2 H) 2.93 (dd, J=13.6, 6.8 Hz, 1 H) 3.00 (dd, J=13.6, 7.3 Hz, 1 H) 4.09 (q, J=7.1 Hz, 2 H) 4.60 - 4.76 (m, 1 H) 6.45 (s, 1 H) 7.24 - 7.40 (m, 4 H) 7.42 - 7.51 (m, 3 H) 7.54 (t, J=1.8 Hz, 1 H).

Example 4-32: 1H NMR (400 MHz, CD3OD) δ ppm 1.20 (t, J=7.2 Hz, 3 H) 2.58 - 2.66 (m, 2 H) 2.68 (s, 3 H) 2.94 (dd, J=14.2, 7.8 Hz, 1 H) 2.99 (dd, J=13.6, 6.8 Hz, 1 H) 4.09 (q, J=7.2 Hz, 2 H) 4.58 - 4.76 (m, 1 H) 7.27 - 7.31 (m, 1 H) 7.33 (d, J=8.3 Hz, 2 H) 7.37 (t, J=7.8 Hz, 1 H) 7.46 - 7.49 (m, 1 H) 7.51 (d, J=8.1 Hz, 2 H) 7.55 (t, J=1.9 Hz, 1 H) 8.06 (s, 1 H) 8.49 (d, J=8.6 Hz, 1 H).

Example 4-33: 1H NMR (400 MHz, CD3OD) δ ppm 1.21 (t, J=7.1 Hz, 3 H) 2.60 - 2.70 (m, 2 H) 2.72 (s, 3 H) 2.97 (dd, J=13.6, 8.1 Hz, 1 H) 3.03 (dd, J=13.9, 6.6 Hz, 1 H) 4.11 (q, J=7.2 Hz, 2 H) 4.67 - 4.81 (m, 1 H) 7.27 - 7.33 (m, 1 H) 7.33 - 7.41 (m, 3 H) 7.48 - 7.52 (m, 1 H) 7.54 (d, J=8.3 Hz, 2 H) 7.57 (t, J=1.8 Hz, 1 H) 8.70 (d, J=8.3 Hz, 1 H) 8.92 (s, 2 H).

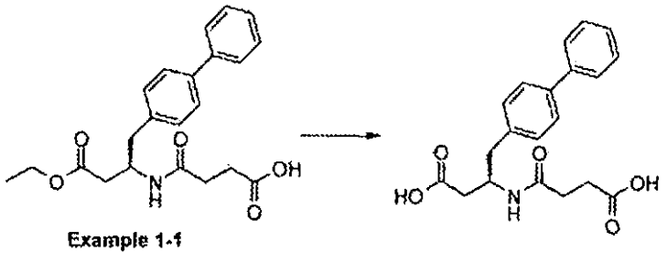
Example 4-34: 1H NMR (400 MHz, CD3OD) δ ppm 1.21 (t, J=7.2 Hz, 3 H) 2.43 (s, 3 H) 2.63 (d, J=6.6 Hz, 2 H) 2.94 (dd, J=13.9, 7.1 Hz, 1 H) 2.99 (dd, J=13.6, 7.6 Hz, 1 H) 4.10 (q, J=7.1 Hz, 2 H) 4.62 - 4.74 (m, 1 H) 7.26 - 7.30 (m, 1 H) 7.30 - 7.39 (m, 3 H) 7.43 - 7.51 (m, 3 H) 7.53 (t, J=1.8 Hz, 1 H) 8.15 (s, 1 H).

Example 4-35: 1H NMR (400 MHz, CD3OD) δ ppm 1.20 (t, J=7.1 Hz, 3 H) 2.64 (dd, J=15.4, 7.3 Hz, 1 H) 2.70 (dd, J=15.9, 6.3 Hz, 1 H) 2.99 (d, J=7.3 Hz, 2 H) 4.10 (q, J=7.2 Hz, 2 H) 4.65 - 4.79 (m, 1 H) 7.14 (dd, J=10.2, 8.7 Hz, 1 H) 7.30 (ddd, J=8.8, 4.1, 2.8 Hz, 1 H) 7.32 - 7.37 (m, 2 H) 7.37 - 7.46 (m, 3 H) 7.67 (s, 1 H) 8.28 (s, 1 H) 8.62 (d, J=8.6 Hz, 1 H).

Example 4-36: 1H NMR (400 MHz, CD3OD) δ ppm 1.20 (t, J=7.2 Hz, 3 H) 1.33 (t, J=7.7 Hz, 3 H) 2.66 (d, J=6.8 Hz, 2 H) 2.83 (q, J=7.6 Hz, 2 H) 2.98 (d, J=7.1 Hz, 2 H) 4.10 (q, J=7.1 Hz, 2 H) 4.65 - 4.79 (m, 1 H) 7.14 (dd, J=10.2, 8.7 Hz, 1 H) 7.30 (ddd, J=8.8, 4.1, 2.8 Hz, 1 H) 7.32 - 7.37 (m, 2 H) 7.37 - 7.46 (m, 3 H) 7.54 (s, 1 H) 8.49 (d, J=8.8 Hz, 1 H).

Example 4-37: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.33 (t, *J*=7.1 Hz, 3 H) 2.22 (s, 3 H) 2.57 - 2.72 (m, 2 H) 2.99 (dd, *J*=13.6, 8.1 Hz, 1 H) 3.16 (dd, *J*=13.6, 6.3 Hz, 1 H) 4.15 - 4.33 (m, 2 H) 4.60 - 4.82 (m, 1 H) 5.55 (s, 1 H) 6.10 (s, 1 H) 7.15 (d, *J*=8.8 Hz, 1 H) 7.34 (d, *J*=8.1 Hz, 3 H) 7.39 (t, *J*=7.7 Hz, 1 H) 7.48 (dt, *J*=7.6, 1.5 Hz, 1 H) 7.54 (d, *J*=8.1 Hz, 2 H) 7.58 (t, *J*=1.8 Hz, 1 H) 7.72 (s, 1 H).

Example 5-1: Synthesis of (R)-4-(biphenyl-4-yl)-3-(3-carboxypropanamido)butanoic acid

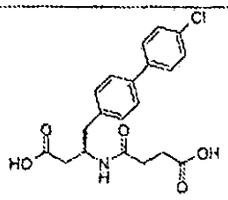
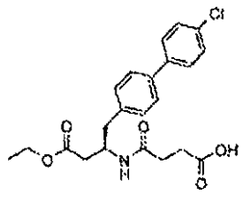
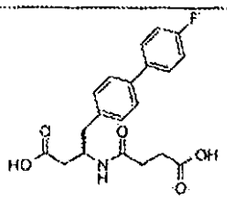
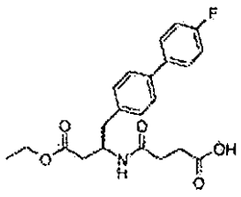
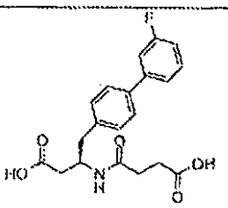
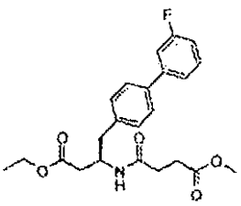
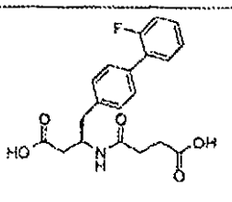
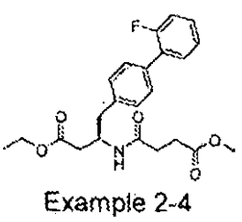


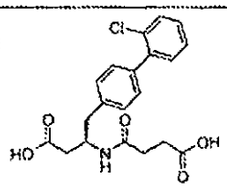
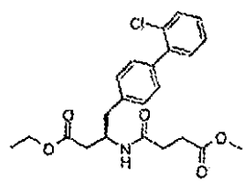
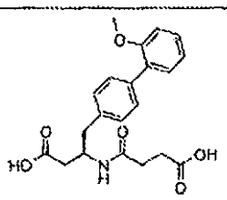
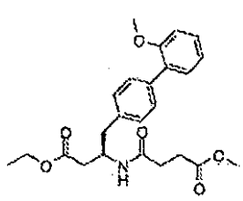
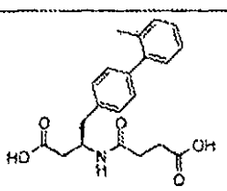
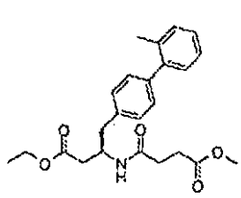
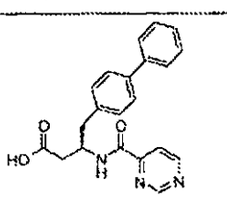
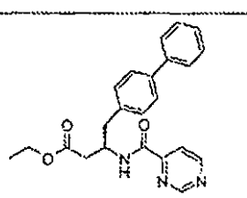
Example 1-1

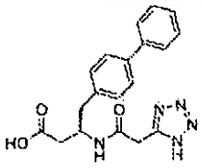
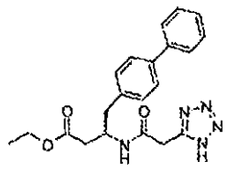
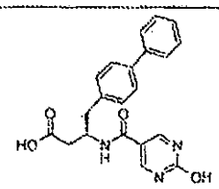
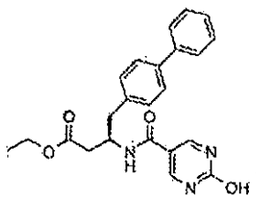
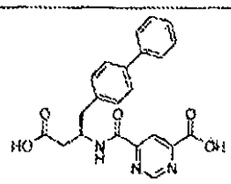
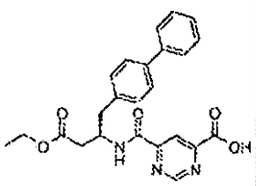
To a solution of (*R*)-4-(1-(biphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid (61.2 mg, 0.160 mmol) in THF (1.6 mL) and methanol (0.2 mL), aqueous 1M NaOH solution (0.638 mL, 0.638 mmol) is added at room temperature. After stirring for 45 minutes, the reaction is quenched with aqueous 0.1 M HCl and is extracted with ethyl acetate. The organic layer is washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give (*R*)-4-(biphenyl-4-yl)-3-(3-carboxypropanamido)butanoic acid (54.9 mg). HPLC retention time = 1.33 minutes (condition A); MS (m+1) = 356.1; 1H NMR (400 MHz, CD3OD) δ ppm 2.40-2.56 (m, 6 H) 2.83 - 2.94 (m, 2 H) 4.43 - 4.50 (m, 1 H) 7.29-7.32 (m, 3 H) 7.41 (t, 2 H, J = 7.7 Hz) 7.53-7.60 (m, 4H).

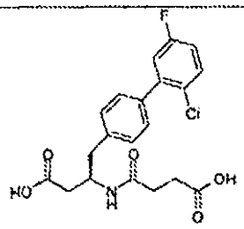
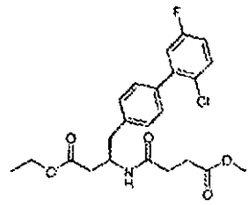
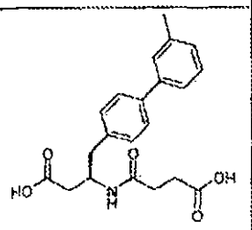
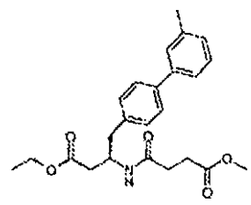
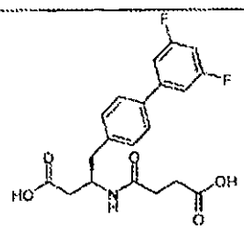
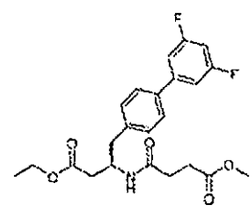
Following compounds are prepared using similar procedure as described in example 5-1:

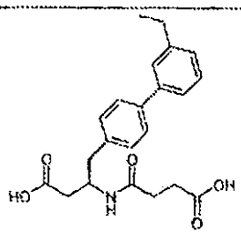
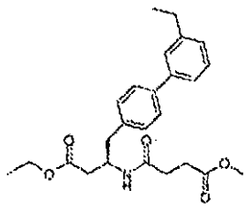
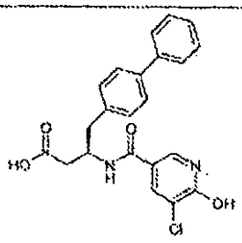
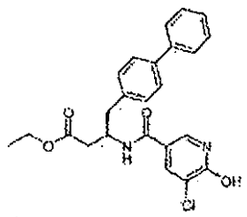
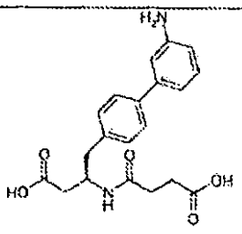
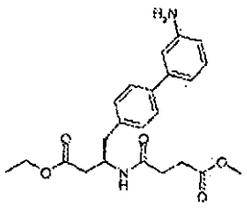
Example #	Product	Starting Material	Hydrolysis Condition	HPLC-RT (condition)	MS (M+1)

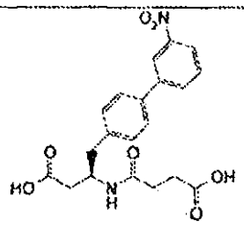
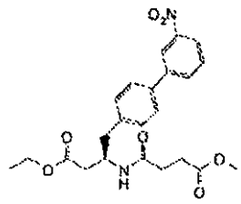
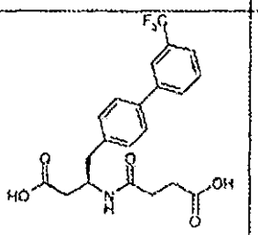
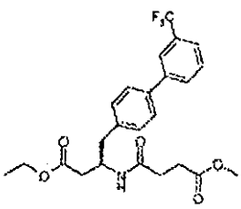
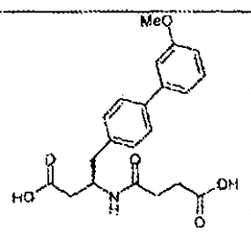
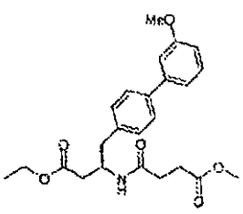
Example 5-2	 (R)-3-(3-carboxy-propionylamino)-4-(4'-chloro-biphenyl-4-yl)-butyric a cid	 Example 2-2	Aq. NaOH, THF, MeOH, rt	1.10 min. (A)	389.9
Example 5-3	 (R)-3-(3-carboxy-propionylamino)-4-(4'-fluoro-biphenyl-4-yl)-butyric a cid	 Example 2-1	Aq. NaOH, THF, MeOH, rt	0.87 min. (A)	373.9
Example 5-4	 (R)-3-(3-carboxy-propionylamino)-4-(3'-fluoro-biphenyl-4-yl)-butyric acid	 Example 2-3	Aq. NaOH, THF, MeOH, rt	0.69 min. (B)	374.0
Example 5-5	 (R)-3-(3-carboxy-propionylamino)-4-	 Example 2-4	Aq. NaOH, THF, MeOH, rt	0.80 min. (B)	373.9

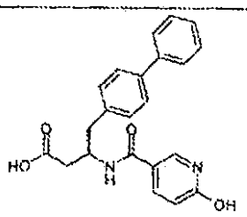
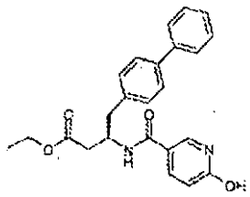
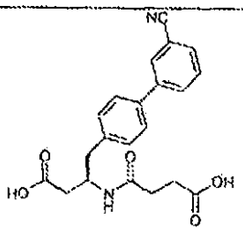
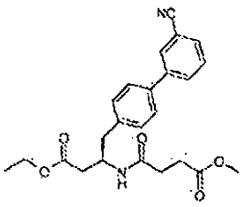
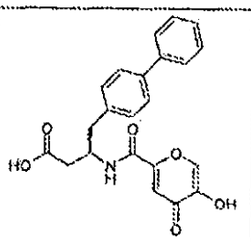
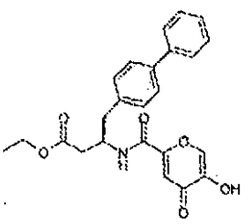
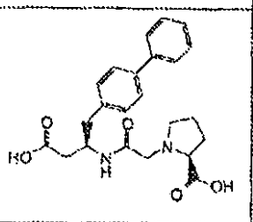
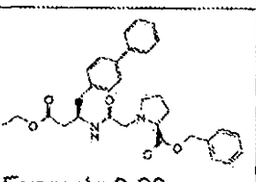
	(2'-fluoro-biphenyl-4-yl)-butyric acid				
Example 5-6	 (R)-3-(3-carboxy-propionylamino)-4-(2'-chloro-biphenyl-4-yl)-butyric acid	 Example 2-5	Aq. NaOH, THF, MeOH, rt	0.74 min. (B)	390.0
Example 5-7	 (R)-3-(3-carboxy-propionylamino)-4-(2'-methoxy-biphenyl-4-yl)-butyric acid	 Example 2-6	Aq. NaOH, THF, MeOH, rt	0.61 min. (B)	386.1
Example 5-8	 (R)-3-(3-carboxy-propionylamino)-4-(2'-methyl-biphenyl-4-yl)-butyric acid	 Example 2-7	Aq. NaOH, THF, MeOH, rt	0.94 min. (B)	370.0
Example 5-9	 (R)-4-biphenyl-4-yl-	 Example 3-3	Aq. LiOH, EtOH, rt.	0.67 min. (B)	362.0

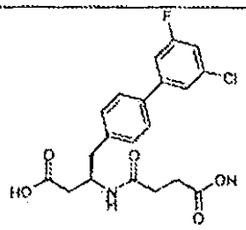
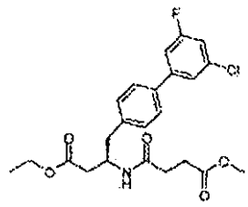
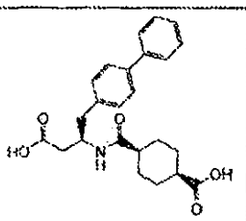
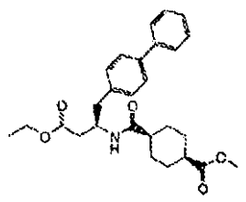
	3-[(pyrimidine-4-carbonyl)-amino]-butyric acid				
Example 5-10	 (R)-4-biphenyl-4-yl-3-(2-1H-tetrazol-5-yl-acetylamino)-butyric acid	 Example 4-1	aq. NaOH, MeOH, RT	1.19 min. (C)	366.0
Example 5-11	 (R)-4-Biphenyl-4-yl-3-[(2-hydroxy-pyrimidine-5-carbonyl)-amino]-butyric acid	 Example 3-2	aq. NaOH, THF, MeOH, RT	1.28 min. (A)	377.9
Example 5-12	 6-((R)-1-Biphenyl-4-ylmethyl-2-carboxy-ethylcarbamoyl)-pyrimidine-4-carboxylic acid	 Example 3-1	aq. NaOH, THF, MeOH, RT	0.80 min. (B)	406.0

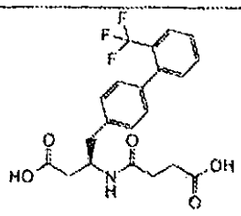
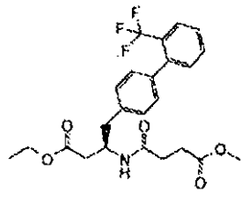
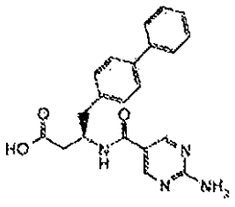
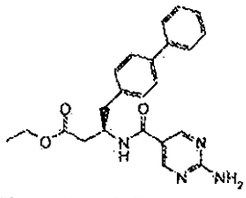
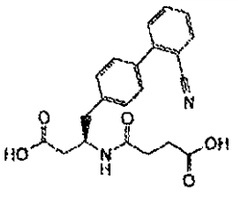
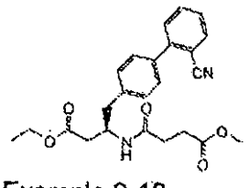
Example 5-13	 (R)-4-(1-carboxy-3-(2'-chloro-5'-fluorobiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-8	aq. NaOH, THF, MeOH, RT	0.74 min. (B)	408.2
Example 5-14	 (R)-4-(1-carboxy-3-(3'-methylbiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-9	aq. NaOH, THF, MeOH, RT	0.55 min. (B)	370.1
Example 5-15	 (R)-4-(1-carboxy-3-(3',5'-difluorobiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-10	aq. NaOH, THF, MeOH, RT	0.46 min. (B)	392.1

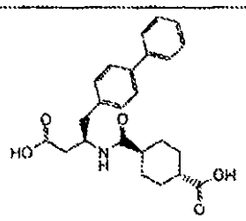
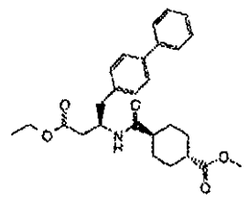
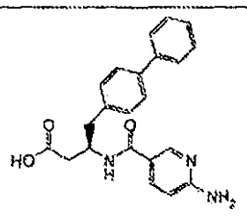
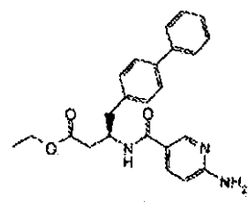
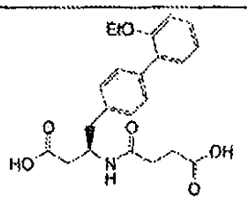
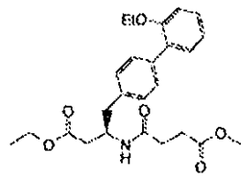
Example 5-16	 (R)-4-(1-carboxy-3-(3'-ethylbiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-11	aq. NaOH, THF, MeOH, RT	0.70 min. (B)	384.3
Example 5-17	 (R)-4-(biphenyl-4-yl)-3-(5-chloro-6-hydroxynicotinamido)butanoic acid	 Example 3-4	aq. NaOH, THF, MeOH, RT	1.40 min. (A)	411.2
Example 5-18	 (R)-4-(3'-aminobiphenyl-4-yl)-3-(3-carboxypropanamido)butanoic acid	 Example 3-20	aq. NaOH, THF, MeOH, RT	0.88 min. (A)	371.2

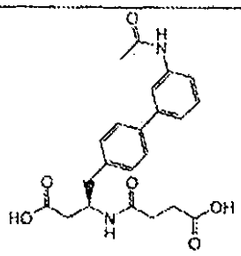
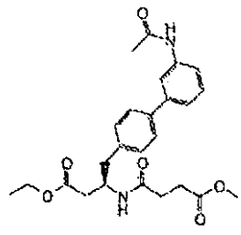
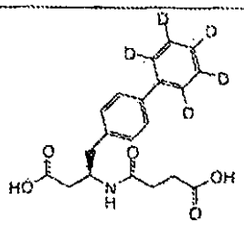
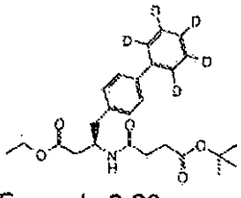
Example 5-19	 (R)-4-(1-carboxy-3-(3'-nitrobiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-12	aq. NaOH, THF, MeOH, RT	1.41 min. (D)	401.2
Example 5-20	 (R)-4-(1-carboxy-3-(3'-(trifluoromethyl)biphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-13	aq. NaOH, THF, MeOH, RT	1.59 min. (H)	424.2
Example 5-21	 (R)-4-(1-carboxy-3-(3'-methoxybiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-14	aq. NaOH, THF, MeOH, RT	1.44 min. (H)	386.2

Example 5-22	 (R)-4-(biphenyl-4-yl)-3-(6-hydroxynicotinamido)butanoic acid	 Example 3-5	aq. NaOH, THF, MeOH, RT	1.29 min. (B)	377.1
Example 5-23	 (R)-4-(1-carboxy-3-(3'-cyanobiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-15	aq. NaOH, THF, MeOH, RT	0.49 min. (B)	381.1
Example 5-24	 (R)-4-(biphenyl-4-yl)-3-(5-hydroxy-4-oxo-4H-pyran-2-carboxamido)butanoic acid	 Example 3-6	aq. NaOH, THF, MeOH, RT	1.36 min. (A)	394.0
Example 5-26		 Example 3-23	aq. NaOH, THF, MeOH, RT	1.20 min. (A)	411.2

	(S)-1-(2-((R)-1-(biphenyl-4-yl)-3-carboxypropan-2-ylamino)-2-oxoethyl)pyrrolidine-2-carboxylic acid trifluoroacetic acid salt				
Example 5-27	 (R)-4-(1-carboxy-3-(3'-chloro-5'-fluorobiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-16	aq. NaOH, THF, MeOH, RT	1.02 min. (B)	408.1
Example 5-28	 (1S,4s)-4-((R)-1-(biphenyl-4-yl)-3-carboxypropan-2-ylcarbamoyl)cyclohexanecarboxylic acid	 Example 3-12	aq. NaOH, THF, MeOH, RT	0.82 min. (B)	410.1

Example 5-29	 (R)-4-(1-carboxy-3-(2'-(trifluoromethyl)biphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-17	aq. NaOH, THF, MeOH, RT	0.53 min. (B)	424.0
Example 5-30	 (R)-3-(2-aminopyrimidine-5-carboxamido)-4-(biphenyl-4-yl)butanoic acid	 Example 3-7	aq. NaOH, THF, MeOH, RT	1.36 min. (A)	377.0
Example 5-31	 (R)-4-(1-carboxy-3-(2'-cyanobiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-18	aq. NaOH, THF, MeOH, RT	1.11 min. (A)	381.1

Example 5-32	 (1R,4r)-4-((R)-1-(biphenyl-4-yl)-3-carboxypropan-2-ylcarbamoyl)cyclohexanecarboxylic acid	 Example 3-13	aq. NaOH, THF, MeOH, RT	0.61 min. (B)	410.1
Example 5-33	 (R)-3-(6-aminonicotinamido)-4-(biphenyl-4-yl)butanoic acid	 Example 3-8	aq. NaOH, THF, MeOH, RT	1.28 min. (A)	376.2
Example 5-34	 (R)-4-(1-carboxy-3-(2'-ethoxybiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-19	aq. NaOH, THF, MeOH, RT	1.51 min. (D)	400.5

Example 5-35	 (R)-4-(3'-acetamidobiphenyl-4-yl)-3-(3-carboxypropanamido)butanoic acid	 Example 3-24	aq. NaOH, THF, MeOH, RT	1.18 min. (D)	413.2
Example 5-36	 (R)-4-(1-carboxy-3-(2',3',4',5',6'-d5-biphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid	 Example 2-20	aq. NaOH, THF, MeOH, 50 °C	0.68 min. (B)	361.2

Example 5-2: 1H NMR (400 MHz, CD3OD) δ ppm 2.38-2.42 (m, 2 H) 2.45 - 2.54 (m, 4 H) 2.82- 2.94 (m, 2 H) 4.42 - 4.48 (m, 1 H) 7.12 - 7.16 (m, 2 H) 7.31 (d, J=8.4 Hz, 2 H) 7.41 (d, J = 8.6 Hz, 2 H) 7.54 (d, J = 8.1 Hz, 2 H) 7.58 (d, J = 8.6 Hz,2 H).

Example 5-3: 1H NMR (400 MHz, CD3OD) δ ppm 2.39-2.42 (m, 2 H) 2.45 - 2.54 (m, 4 H) 2.85 (A of ABX, Jab = 13.6 Hz, Jax = 7.6 HZ, 1 H) 2.91 (B of ABX, Jab = 13.6 Hz, Jbx = 6.2 HZ, 1 H) 4.42 - 4.48 (m, 1 H) 7.12 – 7.16 (m ,2 H) 7.31 (A of AB, J = 8.2 Hz, 2 H) 7.52 (B of AB, J = 8.2 Hz, 2 H) 7.58 – 7.62 (m, 2 H)

Example 5-4: 1H NMR (400 MHz, CD3OD) δ ppm 2.39-2.44 (m, 2 H) 2.46 - 2.55 (m, 4 H) 2.86 (A of ABX, Jab = 13.6 Hz, Jax = 7.6 HZ, 1 H) 2.92 (B of ABX, Jab = 13.6 Hz, Jbx = 6.3

HZ, 1 H) 4.42 - 4.49 (m, 1 H) 7.01 – 7.06 (m ,1 H) 7.32 (br d, J = 8.1 Hz, 2 H) 7.39 – 7.45 (m, 2 H) 7.55 (d, J = 8.1 Hz, 2 H)

Example 5-5: 1H NMR (400 MHz, CD3OD) δ ppm 2.40-2.43 (m, 2 H) 2.46 - 2.56 (m, 4 H) 2.87 (A of ABX, Jab = 13.5 Hz, Jax = 7.7 HZ, 1 H) 2.93 (B of ABX, Jab = 13.5 Hz, Jbx = 6.2 HZ, 1 H) 4.43 - 4.50 (m, 1 H) 7.13 – 7.18 (m, 1 H) 7.20 – 7.24 (m, 1 H) 7.31– 7.35 (m ,3 H) 7.44 – 7.48 (m, 3 H) 7.99 (br d, J = 8.3 Hz, 1 H)

Example 5-6: 1H NMR (400 MHz, CD3OD) δ ppm 2.39-2.43 (m, 2 H) 2.45 - 2.57 (m, 4 H) 2.87 (A of ABX, Jab = 13.6 Hz, Jax = 7.6 HZ, 1 H) 2.94 (B of ABX, Jab = 13.6 Hz, Jbx = 6.1 HZ, 1 H) 4.44 - 4.51 (m, 1 H) 7.28 – 7.35 (m, 7 H) 7.46 (br d, J = 7.9 Hz, 1 H)

Example 5-7: 1H NMR (400 MHz, CD3OD) δ ppm 2.40-2.52 (m, 6 H) 2.83 – 2.92 (m, 2 H) 3.77 (s, 3 H) 4.44 – 4.47 (m, 1 H) 6.96 – 7.05 (m, 2 H) 7.23 – 7.30 (m, 4 H) 7.39 -7.41 (m, 2 H)

Example 5-8: 1H NMR (400 MHz, CD3OD) δ ppm 2.21 (s, 3 H) 2.41-2.55 (m, 6 H) 2.82 – 2.94 (m, 2 H) 3.77 (s, 3 H) 4.45 – 4.48 (m, 1 H) 7.15 – 7.28 (m, 8 H)

Example 5-9: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.56 (dd, J=5.81, 15.92Hz, 1H), 2.66 (dd, J=7.07, 15.92Hz, 1H), 2.90 (dd, J=6.06, 13.64Hz, 1H), 3.00 (dd, J=8.08, 13.64Hz, 1H), 4.53-4.64 (m, 1H), 7.30 (d, J=8.34Hz, 2H), 7.33 (t, J=7.58, 1H), 7.56 (d, J=8.34Hz, 2H), 7.62 (d, J=7.07Hz, 2H), 7.95 (dd, J=1.26, 5.05Hz, 1H), 9.01-9.07 (m, 2H), 9.33 (d, J=1.52Hz, 1H), 12.28 (s, 1H).

Example 5-10: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.36 - 2.49 (m, 2 H), 2.75 - 2.86 (m, 2 H), 3.83 (s, 2 H), 4.19 - 4.31 (m, 1 H), 7.26 (d, J=8.3 Hz, 2 H), 7.31 - 7.38 (m, 1 H), 7.45 (t, J=7.6 Hz, 2 H), 7.56 (d, J=8.3 Hz, 2 H), 7.61 - 7.67 (m, 2 H), 8.40 (d, J=8.1 Hz, 1 H), 12.26 (br. s., 1 H), 16.02 (br. s., 1 H).

Example 5-11: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.46 - 2.59 (m, 2 H), 2.86 - 2.88 (m, 2 H), 4.41 - 4.49 (m, 1 H), 7.29 - 7.36 (m, 3 H), 7.42 – 7.46 (m, 2 H), 7.58 – 7.65 (m, 4 H), 8.26 (d, J=8 Hz, 1 H), 8.64 (br s, 2 H) 12.24 (br. s., 1 H).

Example 5-12: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.54 - 2.70 (m, 2 H), 2.88 – 3.03 (m, 2 H), 4.56 - 4.65 (m, 1 H), 7.29 - 7.34(m, 3 H), 7.41 – 7.45 (m, 2 H), 7.55 – 7.63 (m, 4 H), 8.33 (s, 1 H), 9.15 (d, J = 9.1 Hz, 1 H), 9.49 (s, 1 H), 12.30 (br s, 1 H), 14.11 (br s, 1 H).

Example 5-13: 1H NMR (400 MHz, CD3OD) δ ppm 2.38 - 2.57 (m, 6 H) 2.87 (A of ABX, Jab = 13.6 Hz, Jax = 7.6 Hz, 1 H) 2.95 (B of ABX, Jab = 13.6 Hz, Jbx = 6.1 Hz, 1 H) 4.44 - 4.51 (m, 1 H) 7.06 - 7.14 (m, 2 H) 7.31 - 7.37 (m, 5 H) 7.48 (dd, J = 8.8 and 5.1 Hz, 1 H).

Example 5-14: 1H NMR (400 MHz, CD3OD) δ ppm 2.39 (s, 3 H) 2.39 - 2.55 (m, 6 H) 2.85 (A of ABX, Jab = 13.5 Hz, Jax = 7.5 HZ, 1 H) 2.90 (B of ABX, Jab = 13.5 Hz, Jbx = 6.4 Hz, 1 H) 4.42 – 4.49 (m, 1 H) 7.13 (br d, J = 7.3 Hz, 1 H) 7.26 – 7.30 (m, 3 H) 7.36 - 7.40 (m, 2 H) 7.52 (d, J = 8.3 Hz, 2 H).

Example 5-15: 1H NMR (400 MHz, CD3OD) δ ppm 2.38 - 2.55 (m, 6 H) 2.86 (A of ABX, Jab = 13.6 Hz, Jax = 7.8 HZ, 1 H) 2.93 (B of ABX, Jab = 13.6 Hz, Jbx = 6.1 HZ, 1 H) 4.42 – 4.49 (m, 1 H) 6.86 - 6.92 (m, 1 H) 7.19 - 7.25 (m, 2 H) 7.33 - 7.35 (m, 2 H) 7.55 - 7.58 (m, 2 H).

Example 5-16: 1H NMR (400 MHz, CD3OD) δ ppm 1.27 (t, J = 7.6 Hz, 3 H) 2.39 - 2.55 (m, 6 H) 2.70 (q, J = 7.6 Hz, 2 H) 2.85 (A of ABX, Jab = 13.6 Hz, Jax = 7.5 HZ, 1 H) 2.90 (B of ABX, Jab = 13.6 Hz, Jbx = 6.4 HZ, 1 H) 4.42 – 4.49 (m, 1 H) 7.16 (br d, J= 7.6 Hz, 1 H) 7.28 - 7.33 (m, 3 H) 7.38 - 7.42 (m, 2 H) 7.52 - 7.54 (m, 2 H).

Example 5-17: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.47 - 2.50 (m, 2 H) 2.82 - 2.91 (m, 2 H) 4.40 - 4.49 (m, 1 H) 7.29 (d, J = 8.3 Hz, 2 H) 7.31 - 7.36 (m, 1 H) 7.42 - 7.46 (m, 2 H) 7.59 (d, J = 8.4 Hz, 2 H) 7.63 - 7.65 (m, 2 H) 7.95 (br d, J = 2.3 Hz, 1 H) 8.11 (br d, J = 2.3 Hz, 1 H) 8.25 - 8.27 (m, 1 H) 12.24 (br s, 1 H) 12.48 (br s, 1 H).

Example 5-18: 1H NMR (400 MHz, CD3OD) δ ppm 2.38 - 2.55 (m, 6 H) 2.86 (A of ABX, Jab = 13.6 Hz, Jax = 7.8 Hz, 1 H) 2.92 (B of ABX, Jab = 13.6 Hz, Jbx = 6.3 Hz, 1 H) 4.43 – 4.50 (m, 1 H) 7.26 (br d, J = 7.3 Hz, 1 H) 7.35 (d, J = 8.1 Hz, 2 H) 7.51 – 7.58 (m, 4 H) 7.64 (br d, J = 7.8 Hz, 1 H).

Example 5-19: 1H NMR (400 MHz, CD3OD) δ ppm 2.39 - 2.42 (m, 2 H) 2.45 - 2.56 (m, 4 H) 2.88 (A of ABX, Jab = 13.6 Hz, Jax = 7.6 Hz, 1 H) 2.95 (B of ABX, Jab = 13.6 Hz, Jbx = 6.2

Hz, 1 H) 4.44 – 4.51 (m, 1 H) 6.86 - 6.89 (m, 1 H) 7.38 - 7.41 (m, 2 H) 7.63 - 7.70 (m, 3 H) 8.02 - 8.04 (m, 1 H) 8.18 - 8.21 (m, 1 H) 8.45 (br t, J = 1.9 Hz, 1 H).

Example 5-20: 1H NMR (400 MHz, CD3OD) δ ppm 2.39 - 2.56 (m, 6 H) 2.87 (A of ABX, Jab = 13.6 Hz, Jax = 7.6 Hz, 1 H) 2.93 (B of ABX, Jab = 13.6 Hz, Jbx = 6.3 Hz, 1 H) 4.43 – 4.50 (m, 1 H) 7.36 (d, J = 8.3 Hz, 2 H) 7.58 – 7.62 (m, 4 H) 7.85 - 7.87 (m, 2 H).

Example 5-21: 1H NMR (400 MHz, CD3OD) δ ppm 2.39 - 2.54 (m, 6 H) 2.85 (A of ABX, Jab = 13.6 Hz, Jax = 7.5 Hz, 1 H) 2.91 (B of ABX, Jab = 13.6 Hz, Jbx = 6.3 HZ, 1 H) 3.84 (s, 3 H) 4.42 – 4.49 (m, 1 H) 6.86 - 6.89 (m, 1 H) 7.11 - 7.17 (m, 2 H) 7.29 - 7.34 (m, 3 H) 7.52 - 7.54 (m, 2 H).

Example 5-22: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.43 - 2.46 (m, 2 H), 2.81 - 2.91 (m, 2 H) 4.40 - 4.49 (m, 1 H) 6.33 (d, J = 9.6 Hz, 1 H) 7.28 - 7.35 (m, 3 H) 7.42 - 7.46 (m, 2 H) 7.58 (d, J = 8.1 Hz, 2 H) 7.63 - 7.65 (m, 2 H) 7.81 (dd, J = 9.6, 2.8 Hz, 1 H) 7.93 (br s, 1 H) 8.14 (d, J = 8.3 Hz, 1 H) 11.92 (br s, 1 H) 12.19 (br s, 1 H).

Example 5-23: 1H NMR (400 MHz, CD3OD) δ ppm 2.39 - 2.42 (m, 2 H) 2.44 - 2.55 (m, 4 H) 2.86 (A of ABX, Jab = 13.6 Hz, Jax = 7.6 Hz, 1 H) 2.93 (B of ABX, Jab = 13.6 Hz, Jbx = 6.3 HZ, 1 H) 4.43 – 4.50 (m, 1 H) 7.36 (d, J = 8.3 Hz, 2 H) 7.58 - 7.63 (m, 3 H) 7.66 - 7.69 (m ,1 H) 7.91 - 7.94 (m, 1 H) 7.97 (br t, J = 1.5 Hz, 1 H).

Example 5-24: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.50 - 2.61 (m, 2 H) 2.83 - 2.94 (m, 2 H) 4.43 - 4.52 (m, 1 H) 6.82 (s, 1 H) 7.28 - 7.35 (m, 3 H) 7.44 (t, J = 7.7 Hz, 2 H) 7.58 - 7.65 (m, 4 H) 8.12 (s, 1 H) 8.86 (d, J = 8.3 Hz, 1 H) 9.55 (s, 1 H) 12.25 (br s, 1 H).

Example 5-25: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.66 - 2.47 (m, 10 H) 2.71 - 2.83 (m, 2 H) 3.31 - 3.46 (m, 3 H) 4.18 - 4.49 (m, 2 H) 7.26 - 7.28 (m, 2 H) 7.32 - 7.36 (m, 1 H) 7.43 - 7.47 (m ,2 H) 7.57 - 7.66 (m, 4 H) 7.86 (d, J = 8.3 Hz, 1 H) 12.31 (br s, 2 H).

Example 5-26: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.80 - 2.03 (m, 3 H) 2.27 - 2.31 (m, 1 H) 2.39 - 2.52 (m, 2 H) 2.75 - 2.81 (m, 1 H) 2.85 - 2.89 (m, 1 H) 2.95 - 3.03 (m, 1 H) 3.41 - 3.78 (m, 2 H) 3.90 - 3.99 (m, 1 H) 4.14 - 4.20 (m, 1 H) 4.28 - 4.35 (m, 1 H) 7.28 - 7.37 (m, 3 H) 7.44 - 7.48 (m, 2 H) 7.58 - 7.65 (m ,2 H) 8.45 (br s ,1 H) 12.34 (br s, 1 H).

Example 5-27: 1H NMR (400 MHz, CD3OD) δ ppm 2.38 - 2.54 (m, 6 H) 2.86 (A of ABX, Jab = 13.6 Hz, Jax = 7.6 Hz, 1 H) 2.93 (B of ABX, Jab = 13.6 Hz, Jbx = 6.2 HZ, 1 H) 4.42 – 4.49 (m, 1 H) 7.13 - 7.17 (m, 1 H) 7.31 - 7.37 (m ,3 H) 7.46 - 7.47 (m, 1 H) 7.54 - 7.57 (m, 2 H).

Example 5-28: 1H NMR (400 MHz, CD3OD) δ ppm 1.49 - 1.71 (m, 6 H) 2.01 - 2.11 (m, 2 H) 2.14 - 2.21 (m, 1 H) 2.44 - 2.56 (m, 3 H) 2.83 (A of ABX, Jab = 13.6 Hz, Jax = 8.0 Hz, 1 H) 2.91 (B of ABX, Jab = 13.6 Hz, Jbx = 6.3 HZ, 1 H) 4.43 – 4.51 (m, 1 H) 7.28 - 7.32 (m, 3 H) 7.38 - 7.42 (m ,2 H) 7.52 (d, J = 8.1 Hz, 2 H) 7.56 - 7.59 (m, 2 H) 7.71 (br d, J = 8.6 Hz, 1 H).

Example 5-29: 1H NMR (400 MHz, CD3OD) δ ppm 2.39 - 2.42 (m, 2 H) 2.45 - 2.56 (m, 4 H) 2.87 (A of ABX, Jab = 13.6 Hz, Jax = 7.8 Hz, 1 H) 2.94 (B of ABX, Jab = 13.6 Hz, Jbx = 6.1 Hz, 1 H) 4.44 – 4.51 (m, 1 H) 7.23 (A of AB, J = 8.0 Hz, 2 H) 7.28 (B of AB, J = 8.0 Hz, 2 H) 7.35 (d, J = 7.6 Hz, 1 H) 7.50 - 7.53 (m, 1 H) 7.60 - 7.63 (m, 1 H) 7.75 (d, J = 7.8 Hz, 1 H)

Example 5-30: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.45 - 2.56 (m, 2 H) 2.83 - 2.93 (m, 2 H) 4.43 - 4.52 (m, 1 H) 7.18 (s, 2 H) 7.29 - 7.35 (m, 3 H) 7.42 - 7.46 (m, 2 H) 7.58 - 7.65 (m, 4 H) 8.19 (d, J = 8.1 Hz, 1 H) 8.60 (s, 2 H) 12.21 (br s, 1 H).

Example 5-31: 1H NMR (400 MHz, CD3OD) δ ppm 2.39 - 2.43 (m, 2 H) 2.46 - 2.57 (m, 4 H) 2.90 (A of ABX, Jab = 13.6 Hz, Jax = 7.8 Hz, 1 H) 2.97 (B of ABX, Jab = 13.6 Hz, Jbx = 6.1 Hz, 1 H) 4.45 – 4.52 (m, 1 H) 7.37 - 7.39 (m, 2 H) 7.49 - 7.53 (m, 3 H) 7.57 - 7.59 (m ,1 H) 7.70 - 7.74 (m, 1 H) 7.80 - 7.82 (m, 1 H).

Example 5-32: 1H NMR (400 MHz, CD3OD) δ ppm 1.33 - 1.49 (m, 4 H) 1.68 - 1.72 (m, 1 H) 1.79 - 1.83 (m, 1 H) 1.96 - 2.01 (m, 2 H) 2.05 - 2.13 (m, 1 H) 2.17 - 2.25 (m, 1 H) 2.43 - 2.55 (m, 2 H) 2.80 - 2.95 (m, 2 H) 4.42 - 4.49 (m, 1 H) 7.28 - 7.32 (m, 3 H) 7.38 - 7.43 (m, 2 H) 7.52 - 7.59 (m, 4 H).

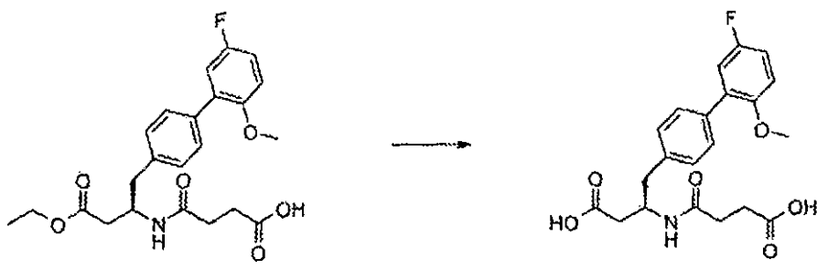
Example 5-33: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.48 - 2.55 (m, 2 H) 2.84 - 2.96 (m, 2 H) 4.44 - 4.53 (m, 1 H) 6.94 (br s, 1 H) 7.30 - 7.35 (m, 3 H) 7.42 - 7.46 (m, 2 H) 7.57 - 7.64 (m, 4 H) 8.17 - 8.60 (br m, 5 H) 12.27 (br s, 1 H).

Example 5-34: 1H NMR (400 MHz, CD3OD) δ ppm 1.30 (t, J = 7.0 Hz, 3 H) 2.39 - 2.56 (m, 6 H) 2.82 - 2.93 (m, 2 H) 4.02 (q, J = 7.0 Hz, 2 H) 4.42 – 4.49 (m, 1 H) 6.96 - 7.03 (m, 2 H) 7.23 - 7.28 (m, 4 H) 7.44 (d, J = 8.4 Hz, 2 H).

Example 5-35: 1H NMR (400 MHz, CD3OD) δ ppm 2.14 (s, 3 H) 2.39 - 2.43 (m, 2 H) 2.45-2.56 (m, 4 H) 2.82 - 2.94 (m, 2 H) 4.02 (q, J = 7.0 Hz, 2 H) 4.42 – 4.49 (m, 1 H) 7.30 - 7.38 (m, 4 H) 7.49 - 7.55 (m, 3 H) 7.80 (br s, 1 H).

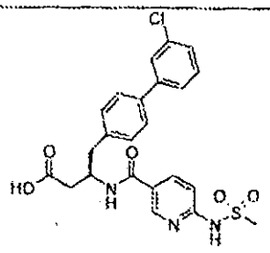
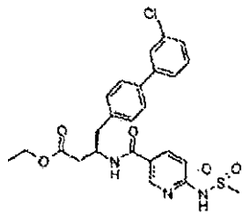
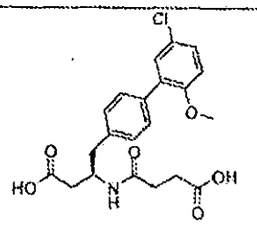
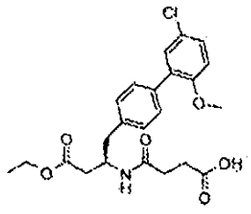
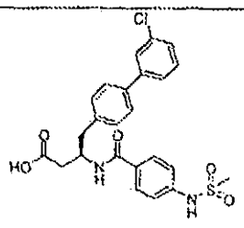
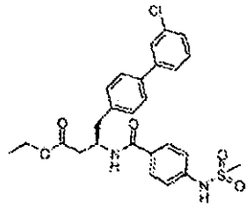
Example 5-36: 1H NMR (400 MHz, CD3OD) δ ppm 2.39 - 2.55 (m, 6 H) 2.85 (A of ABX, Jab = 13.6 Hz, Jax = 7.5 HZ, 1 H) 2.90 (B of ABX, Jab = 13.6 Hz, Jbx = 6.3 HZ, 1 H) 4.42 – 4.49 (m, 1 H) 6.86 - 6.92 (m, 1 H) 7.31 (d, J = 8.1 Hz, 2 H) 7.53 - 7.55 (m, 2 H).

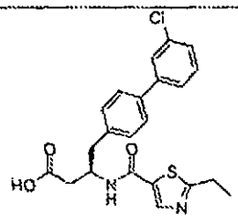
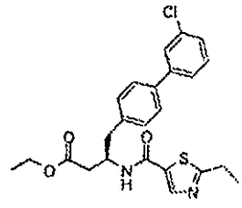
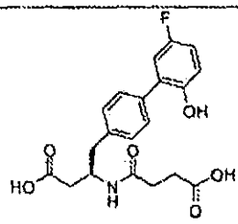
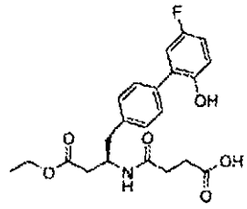
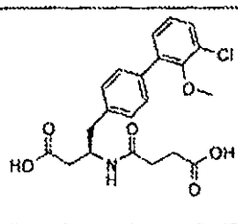
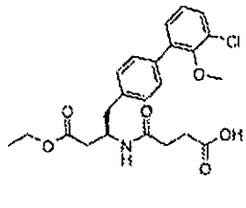
Example 5-37: Synthesis of (R)-4-(1-carboxy-3-(5'-fluoro-2'-methoxybiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid

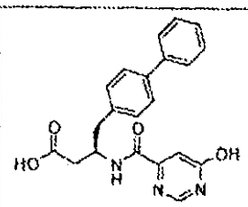
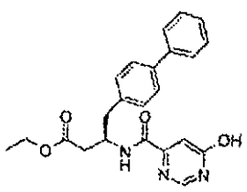
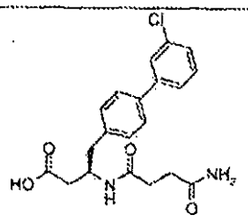
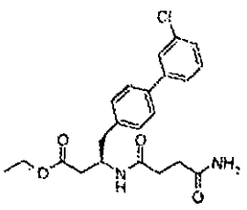
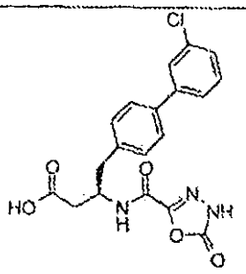
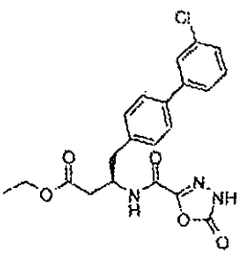


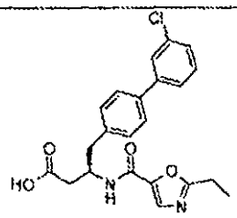
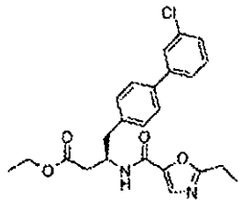
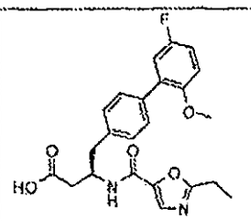
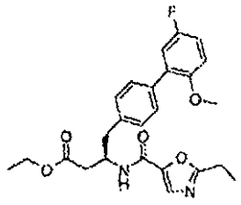
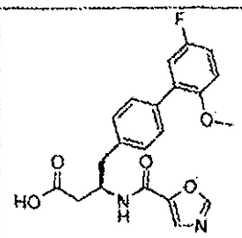
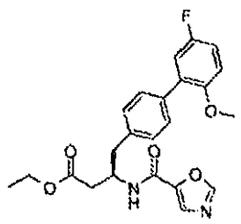
To a solution of (R)-4-(4-ethoxy-1-(5'-fluoro-2'-methoxybiphenyl-4-yl)-4-oxobutan-2-ylamino)-4-oxobutanoic acid (83 mg, 0.192 mmol) in MeOH (2 mL) is added 1N NaOH (4 mL, 4 mmol) After stirring at room temperature for 2 hours, the crude is concentrated under reduced pressure to remove MeOH and is diluted with EtOAc. The organic layer is washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue is purified by RP-HPLC (SunFire C18, H_2O(0.1% TFA)/CH_3CN), and then lyophilized to give (R)-4-(1-carboxy-3-(5'-fluoro-2'-methoxybiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid (58 mg). HPLC retention time = 1.46 minutes (condition D); MS (m+1) = 404.2; 1H NMR (400 MHz, CD_3OD) δ ppm 2.36 - 2.59 (m, 6 H) 2.84 (dd, *J*=13.4, 6.3 Hz, 1 H) 2.91 (dd, *J*=13.4, 6.3 Hz, 1 H) 3.75 (s, 3 H) 4.34 - 4.56 (m, 1 H) 6.95 - 7.08 (m, 3 H) 7.26 (d, *J*=8.1 Hz, 2 H) 7.42 (d, *J*=8.3 Hz, 2 H)

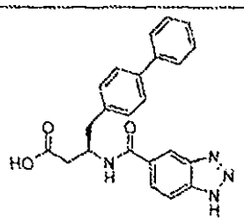
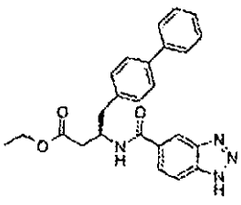
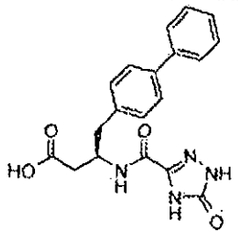
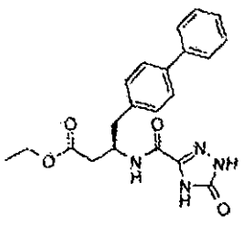
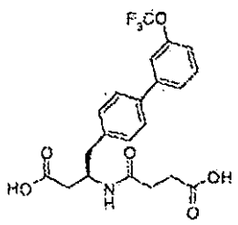
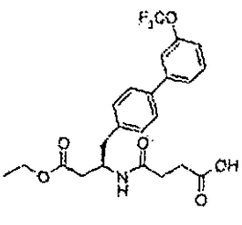
Following compounds are prepared using similar procedure as described in example 5-37:

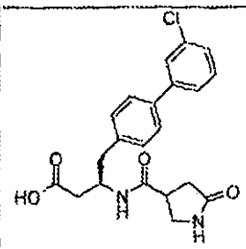
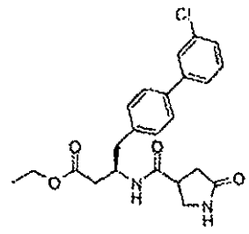
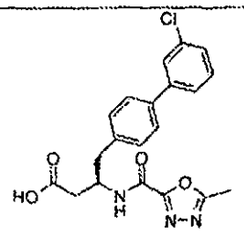
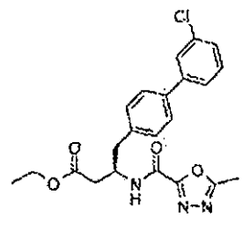
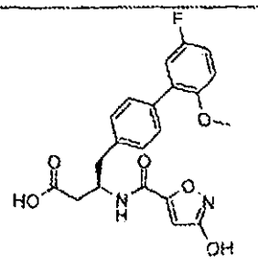
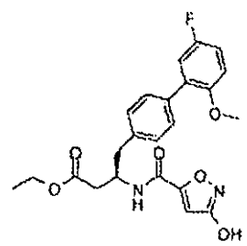
Example #	Product	Starting Material	Hydrolysis Condition	LCMS-RT (condition)	MS (M+1)
Example 5-38	 R-4-(3'-chlorobiphenyl-4-yl)-3-(6-(methylsulfonamido)nicotinamido)butanoic acid		Aq. NaOH, MeOH, rt	1.68 min. (D)	488.1
Example 5-39	 R-4-(1-carboxy-3-(5'-chloro-2'-methoxybiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid		Aq. NaOH, MeOH, rt	1.52 min. (D)	420.1
Example 5-40	 R-4-(3'-chlorobiphenyl-4-yl)-3-(4-(methylsulfonamido)benzamido)butanoic		Aq. NaOH, MeOH, rt	1.57 min. (D)	487.2

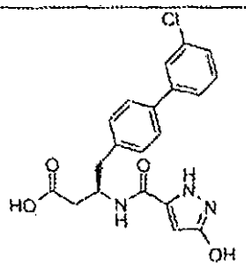
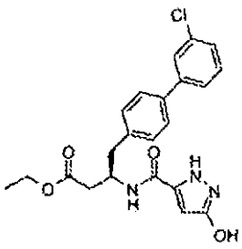
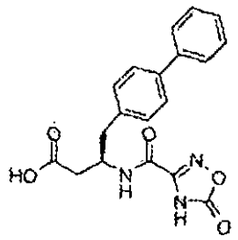
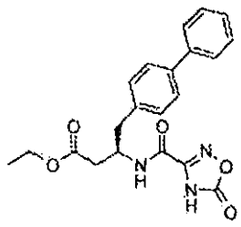
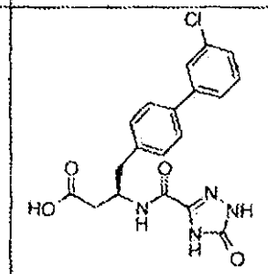
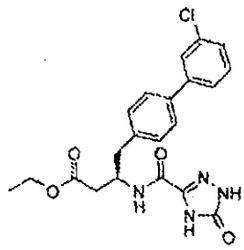
	acid				
Example 5-41	 R-4-(3'-chlorobiphenyl-4-yl)-3-(2-ethylthiazole-5-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.65 min. (D)	429.1
Example 5-42	 R-4-(1-carboxy-3-(5'-fluoro-2'-hydroxybiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid		Aq. NaOH, MeOH, rt	1.42 min. (D)	390.2
Example 5-43	 R-4-(1-carboxy-3-(3'-chloro-2'-methoxybiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid		Aq. NaOH, MeOH, rt	1.53 min. (D)	420.2

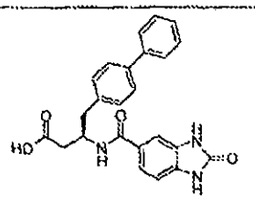
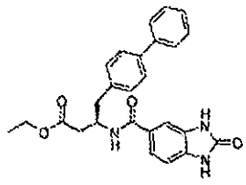
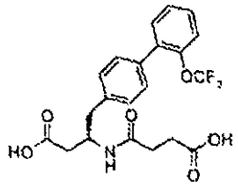
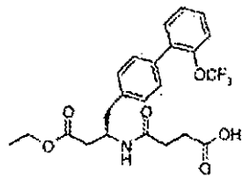
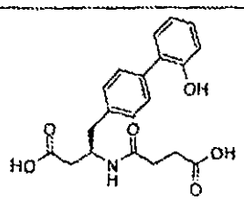
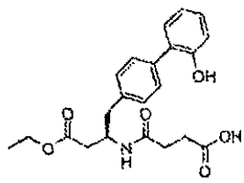
Example 5-44	 R-4-(biphenyl-4-yl)-3-(6-hydroxypyrimidine-4-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.45 min. (D)	378.1
Example 5-45	 (R)-3-(4-amino-4-oxobutanamido)-4-(3'-chlorobiphenyl-4-yl)butanoic acid		Aq. NaOH, MeOH, rt	1.26 min. (A)	389.3
Example 5-46	 R-4-(3'-chlorobiphenyl-4-yl)-3-(5-oxo-4,5-dihydro-1,3,4-oxadiazole-2-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.53 min. (D)	402.2

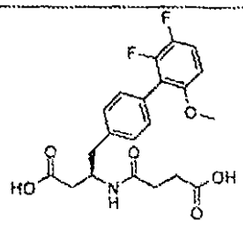
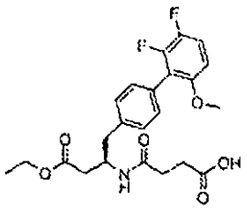
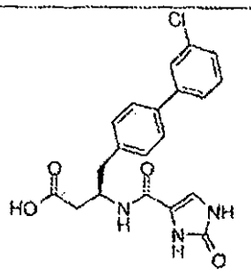
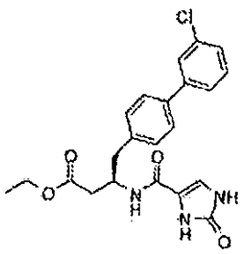
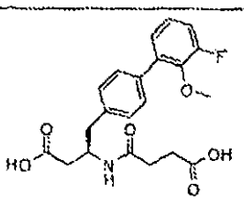
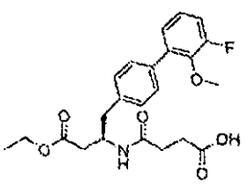
Example 5-47	 R-4-(3'-chlorobiphenyl-4-yl)-3-(2-ethyloxazole-5-carboxamido)butanoic acid		Aq. NaOH, MeOH, *rt*	1.60 min. (D)	413.3
Example 5-48	 R-3-(2-ethyloxazole-5-carboxamido)-4-(5'-fluoro-2'-methoxybiphenyl-4-yl)butanoic acid		Aq. NaOH, MeOH, rt	1.38 min. (D)	427.2
Example 5-49	 R-4-(5'-fluoro-2'-methoxybiphenyl-4-yl)-3-(oxazole-5-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.37 min. (D)	399.3

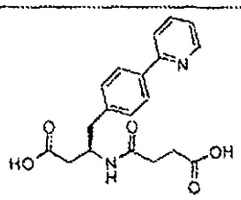
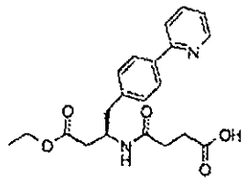
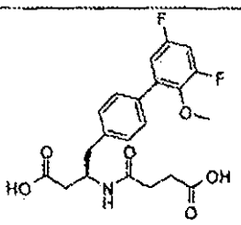
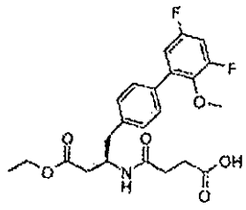
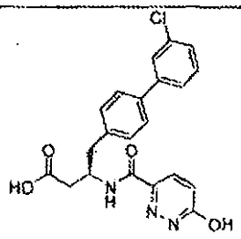
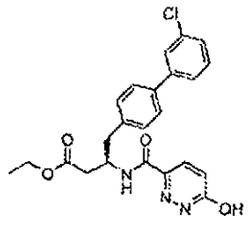
Example 5-50	 R-3-(1H-benzo[d][1,2,3]triazole-5-carboxamido)-4-(biphenyl-4-yl)butanoic acid		Aq. NaOH, MeOH, rt	1.50 min. (D)	401.1
Example 5-51	 R-4-(biphenyl-4-yl)-3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.39 min. (D)	367.1
Example 5-52	 R-4-(1-carboxy-3-(3'-(trifluoromethoxy)biphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid		Aq. NaOH, MeOH, rt	1.57 min. (D)	440.1

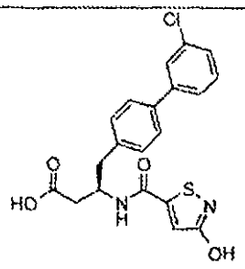
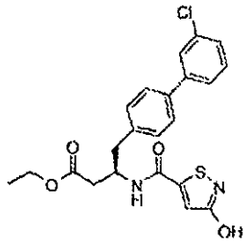
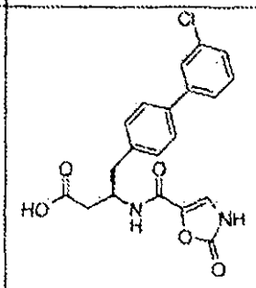
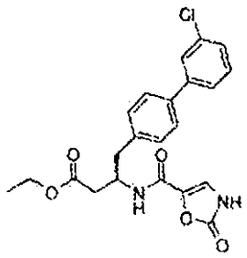
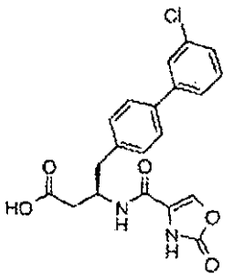
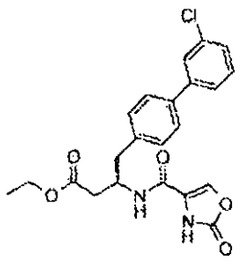
Example 5-53	 (3R)-4-(3'-chlorobiphenyl-4-yl)-3-(5-oxopyrrolidine-3-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.37 min. (D)	401.3
Example 5-54	 R-4-(3'-chlorobiphenyl-4-yl)-3-(5-methyl-1,3,4-oxadiazole-2-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.44 min. (D)	400.2
Example 5-55	 R-4-(5'-fluoro-2'-methoxybiphenyl-4-yl)-3-(3-hydroxyisoxazole-5-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.37 min. (D)	415.1

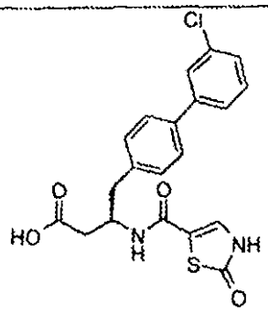
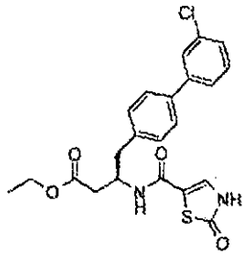
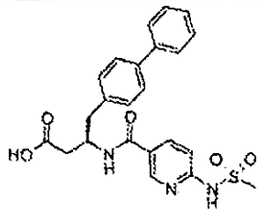
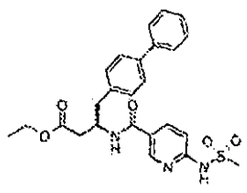
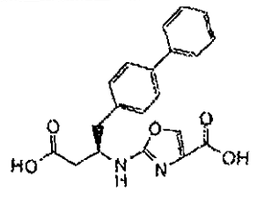
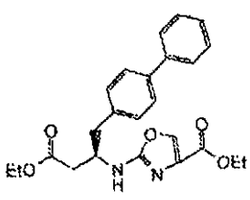
Example 5-56	 R-4-(3'-chlorobiphenyl-4-yl)-3-(3-hydroxy-1H-pyrazole-5-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.52 min. (D)	400.2
Example 5-57	 R-4-(biphenyl-4-yl)-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazole-3-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.77 min. (D)	368.2
Example 5-58	 R-4-(3'-chlorobiphenyl-4-yl)-3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-carboxamido)butanoi		Aq. NaOH, MeOH, rt	1.63 min. (D)	401.1

	c acid				
Example 5-59	 R-4-(biphenyl-4-yl)-3-(2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.46 min. (D)	416.0
Example 5-60	 R-4-(1-carboxy-3-(2'-(trifluoromethoxy)biphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid		Aq. NaOH, MeOH, rt	1.41 min. (D)	440.0
Example 5-61	 R-4-(1-carboxy-3-(2'-hydroxybiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid		Aq. NaOH, MeOH, rt	1.16 min. (D)	372.2

Example 5-62	 R-4-(1-carboxy-3-(2',3'-difluoro-6'-methoxybiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid		Aq. NaOH, MeOH, rt	1.34 min. (D)	422.2
Example 5-63	 R-4-(3'-chlorobiphenyl-4-yl)-3-(2-oxo-2,3-dihydro-1H-imidazole-4-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.16 min. (D)	400.1
Example 5-64	 R-4-(1-carboxy-3-(3'-fluoro-2'-methoxybiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid		Aq. NaOH, MeOH, rt	1.29 min. (D)	404.1

Example 5-65	 R-4-(1-carboxy-3-(4-pyridine-2-yl)phenyl)propan-2-ylamino)-4-oxobutanoic acid		Aq. NaOH, MeOH, rt	1.43 min. (D)	356.2
Example 5-66	 R-4-(1-carboxy-3-(3',5'-difluoro-2'-methoxybiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid		Aq. NaOH, MeOH, rt	1.42 min. (D)	422.0
Example 5-67	 R-4-(3'-chlorobiphenyl-4-yl)-3-(6-hydroxypyridazine-3-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.78 min. (D)	412.1

Example 5-68	 R-4-(3'-chlorobiphenyl-4-yl)-3-(3-hydroxyisothiazole-5-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.53 min. (D)	417.1
Example 5-69	 R-4-(3'-chlorobiphenyl-4-yl)-3-(2-oxo-2,3-dihydrooxazole-5-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.79 min. (D)	401.2
Example 5-70	 R-4-(3'-chlorobiphenyl-4-yl)-		Aq. NaOH, MeOH, rt	1.62 min. (D)	401.1

	3-(2-oxo-2,3-dihydrooxazole-4-carboxamido)butanoic acid				
Example 5-71	 R-4-(3'-chlorobiphenyl-4-yl)-3-(2-oxo-2,3-dihydrothiazole-5-carboxamido)butanoic acid		Aq. NaOH, MeOH, rt	1.73 min. (D)	417.2
Example 5-72	 R-4-(biphenyl-4-yl)-3-(6-(methylsulfonamido)nicotinamido)butanoic acid		Aq. NaOH, MeOH, rt	1.49 min. (D)	454.2
Example 5-73	 2-((R)-1-Biphenyl-4-ylmethyl-2-carboxy-		Aq. NaOH, EtOH, rt	1.28 min. (A)	367.0

	ethylamino)-oxazole-4-carboxylic acid				

Example 5-38: 1H NMR (400 MHz, CD3OD) δ ppm 2.65 (d, *J*=7.1 Hz, 2 H) 2.91 - 3.07 (m, 2 H) 3.26 (s, 3 H) 4.70 (m, 1 H) 7.04 (d, *J*=8.8 Hz, 1 H) 7.26 - 7.33 (m, 1 H) 7.33 - 7.44 (m, 3 H) 7.47 - 7.56 (m, 3 H) 7.57 (t, *J*=1.9 Hz, 1 H) 8.02 (dd, *J*=8.8, 2.5 Hz, 1 H) 8.55 (d, *J*=1.78 Hz, 1 H).

Example 5-39: 1H NMR (400 MHz, CD_3OD) δ ppm 2.36 - 2.60 (m, 6 H) 2.84 (dd, *J*=13.4, 6.1 Hz, 1 H) 2.91 (dd, *J*=13.4, 6.1 Hz, 1 H) 3.77 (s, 3 H) 4.34 - 4.58 (m, 1 H) 7.03 (d, *J*=8.6 Hz, 1 H) 7.18 - 7.31 (m, 4 H) 7.39 (d, *J*=8.1 Hz, 2 H)

Example 5-40: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 - 2.70 (m, 2 H) 2.79 - 2.99 (m, 2 H) 3.05 (s, 3 H) 4.41 - 4.62 (m, 1 H) 7.22 (d, *J*=8.8 Hz, 2 H) 7.33 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.43 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.56 - 7.66 (m, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 7.76 (d, *J*=8.6 Hz, 2 H) 8.30 (d, *J*=8.3 Hz, 1 H) 10.09 (s, 1 H) 12.24 (s, 1 H)

Example 5-41: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (t, *J*=7.6 Hz, 3 H) 2.51 - 2.60 (m, 2 H) 2.84 - 2.94 (m, 2 H) 2.97 (q, *J*=7.6 Hz, 2 H) 4.36 - 4.56 (m, 1 H) 7.32 (d, *J*=8.3 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.60 - 7.66 (m, 3 H) 7.70 (t, *J*=1.8 Hz, 1 H) 8.23 (s, 1 H) 8.60 (d, *J*=8.3 Hz, 1 H) 12.30 (br. s., 1 H)

Example 5-42: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.23 - 2.31 (m, 2 H) 2.31 - 2.43 (m, 4 H) 2.76 (d, *J*=6.6 Hz, 2 H) 4.16 - 4.30 (m, 1 H) 6.87 - 7.02 (m, 2 H) 7.07 (dd, *J*=9.6, 3.0 Hz, 1 H) 7.21 (d, *J*=8.3 Hz, 2 H) 7.50 (d, *J*=8.1 Hz, 2 H) 7.90 (d, *J*=8.1 Hz, 1 H) 9.51 (br. s., 1 H)

Example 5-43: 1H NMR (400 MHz, CD_3OD) δ ppm 2.33 - 2.60 (m, 6 H) 2.85 (dd, *J*=13.7, 6.1 Hz, 1 H) 2.94 (dd, *J*=13.7, 6.1 Hz, 1 H) 3.45 (s, 3 H) 4.35 - 4.57 (m, 1 H) 7.14 (t, *J*=7.8 Hz, 1 H) 7.21 - 7.34 (m, 3 H) 7.38 (dd, *J*=8.0, 1.6 Hz, 1 H) 7.47 (d, *J*=8.3 Hz, 2 H)

Example 5-44: 1H NMR (400 MHz, CD_3OD) δ ppm 2.64 (d, *J*=5.8 Hz, 2 H) 3.01 (d, *J*=6.8 Hz, 2 H) 4.51 - 4.74 (m, 1 H) 7.00 (br. s., 1 H) 7.25 - 7.35 (m, 3 H) 7.40 (t, *J*=7.6 Hz, 2 H) 7.53 (d, *J*=8.1 Hz, 2 H) 7.58 (d, *J*=8.1 Hz, 2 H) 8.21 (br. s., 1 H)

Example 5-45: 1H NMR (400 MHz, CD_3OD) δ ppm 2.38 - 2.55 (m, 6 H) 2.85 (dd, *J*=13.6, 6.3, Hz, 1 H) 2.93 (dd, *J*=13.6, 6.3, Hz, 1 H) 4.40 - 4.56 (m, 1 H) 7.27 - 7.37 (m, 3 H) 7.40 (t, *J*=7.8 Hz, 1 H) 7.54 - 7.56 (m, 3 H) 7.60 (t, *J*=1.8 Hz, 1 H)

Example 5-46: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 - 2.63 (m, 2 H) 2.84 (dd, *J*=13.6, 8.3 Hz, 1 H) 2.89 (dd, *J*=13.6, 8.3 Hz, 1 H) 4.40 - 4.55 (m, 1 H) 7.30 (d, *J*=8.3 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.58 - 7.66 (m, 3 H) 7.70 (t, *J*=1.9 Hz, 1 H) 8.95 (d, *J*=8.6 Hz, 1 H) 12.93 (s, 1 H)

Example 5-47: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (t, *J*=7.6 Hz, 3 H) 2.51 - 2.59 (m, 2 H) 2.80 (q, *J*=7.6 Hz, 2 H) 2.84 - 2.94 (m, 2 H) 4.41 - 4.56 (m, 1 H) 7.31 (d, *J*=8.1 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.59 (s, 1 H) 7.63 (d, *J*=8.3 Hz, 3 H) 7.70 (t, *J*=1.9 Hz, 1 H) 8.45 (d, *J*=8.6 Hz, 1 H) 12.27 (br. s., 1 H)

Example 5-48: 1H NMR (400 MHz, CD_3OD) δ ppm 1.33 (t, *J*=7.6 Hz, 3 H) 2.64 (d, *J*=6.8 Hz, 2 H) 2.84 (q, *J*=7.6 Hz, 2 H) 2.98 (d, *J*=7.01 Hz, 2 H) 3.72 (s, 3 H) 4.62 - 4.75 (m, 1 H) 6.94 - 7.06 (m, 3 H) 7.27 (d, *J*=8.1 Hz, 2 H) 7.40 (d, *J*=8.3 Hz, 2 H) 7.54 (s, 1 H)

Example 5-49: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 - 2.62 (m, 2 H) 2.84 (dd, *J*=13.7, 7.9 Hz, 1 H) 2.91 (dd, *J*=13.7, 7.9 Hz, 1 H) 3.73 (s, 3 H) 4.42 - 4.55 (m, 1 H) 7.05 - 7.19 (m, 3 H) 7.25 (d, *J*=8.1 Hz, 2 H) 7.42 (d, *J*=8.1 Hz, 2 H) 7.73 (s, 1 H) 8.55 (s, 1 H) 8.63 (d, *J*=8.6 Hz, 1 H)

Example 5-50: 1H NMR (400 MHz, CD_3OD) δ ppm 2.69 (d, *J*=6.8 Hz, 2 H) 2.95 - 3.10 (m, 2 H) 4.68 - 4.79 (m, 1 H) 7.21 - 7.33 (m, 1 H) 7.33 - 7.47 (m, 4 H) 7.49 - 7.65 (m, 4 H) 7.76 - 7.97 (m, 2 H) 8.20 - 8.42 (m, 1 H)

Example 5-51: 1H NMR (400 MHz, CD_3OD) δ ppm 2.62 (d, *J*=6.6 Hz, 2 H) 2.96 (d, *J*=7.3 Hz, 2 H) 4.54 - 4.68 (m, 1 H) 7.28 - 7.36 (m, 3 H) 7.40 (t, *J*=7.7 Hz, 2 H) 7.56 (dd, *J*=17.2, 7.8 Hz, 4 H)

Example 5-52: 1H NMR (400 MHz, CD_3OD) δ ppm 2.34 - 2.45 (m, 2 H) 2.45 - 2.59 (m, 4 H) 2.86 (dd, *J*=13.4, 6.0 Hz, 1 H) 2.93 (dd, *J*=13.4, 6.0 Hz, 1 H) 4.40 - 4.55 (m, 1 H) 7.19 - 7.26

(m, 1 H) 7.34 (d, *J*=8.1 Hz, 2 H) 7.46 - 7.49 (m, 1 H) 7.51 (t, *J*=8.0 Hz, 1 H) 7.56 (d, *J*=8.3 Hz, 2 H) 7.61 (d, *J*=7.8 Hz, 1 H)

Example 5-53: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.04 - 2.26 (m, 2 H) 2.31 - 2.46 (m, 2 H) 2.69 - 2.88 (m, 2 H) 2.94 - 3.21 (m, 2 H) 4.18 - 4.37 (m, 1 H) 7.28 (d, *J*=7.1 Hz, 2 H) 7.35 - 7.43 (m, 1 H) 7.43 - 7.54 (m, 2 H) 7.63 (d, *J*=8.2 Hz, 3 H) 7.70 (t, *J*=1.9 Hz, 1 H) 7.98 (dd, *J*=8.3, 2.3 Hz, 1 H) 12.22 (br. s., 1 H)

Example 5-54: 1H NMR (400 MHz, CD_3OD) δ ppm 2.57 (s, 3 H) 2.68 (d, *J*=6.6 Hz, 2 H) 2.92 - 3.08 (m, 2 H) 4.64 - 4.74 (m, 1 H) 7.25 - 7.33 (m, 1 H) 7.33 - 7.44 (m, 3 H) 7.44 - 7.55 (m, 3 H) 7.57 (t, *J*=1.8 Hz, 1 H)

Example 5-55: 1H NMR (400 MHz, CD_3OD) δ ppm 2.64 (d, *J*=6.3 Hz, 2 H) 2.97 (d, *J*=7.1 Hz, 2 H) 3.74 (s, 3 H) 4.58 - 4.73 (m, 1 H) 6.43 (s, 1 H) 6.96 - 7.08 (m, 3 H) 7.27 (d, *J*=8.1 Hz, 2 H) 7.42 (d, *J*=8.1 Hz, 2 H) 8.71 (d, *J*=8.3 Hz, 1 H)

Example 5-56: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 - 2.67 (m, 2 H) 2.80 - 2.96 (m, 2 H) 4.38 - 4.54 (m, 1 H) 5.90 (br. s., 1 H) 7.30 (d, *J*=8.1 Hz, 2 H) 7.35 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.61 (d, *J*=8.3 Hz, 3 H) 7.69 (t, *J*=1.9 Hz, 1 H) 8.08 (br. s., 1 H)

Example 5-57: 1H NMR (400 MHz, CD_3OD) δ ppm 2.48 - 2.55 (m, 1 H) 2.64 (d, *J*=6.8 Hz, 1 H) 2.88 - 3.00 (m, 2 H) 4.32 - 4.69 (m, 1 H) 7.26 - 7.35 (m, 3 H) 7.41 (t, *J*=7.5 Hz, 2 H) 7.49 - 7.65 (m, 4 H)

Example 5-58: 1H NMR (400 MHz, CD_3OD) δ ppm 2.62 (d, *J*=6.6 Hz, 2 H) 2.92 - 3.01 (m, 2 H) 4.59 - 4.64 (m, 1 H) 7.28 - 7.43 (m, 4 H) 7.48 - 7.56 (m, 3 H) 7.59 (t, *J*=1.9 Hz, 1 H)

Example 5-59: 1H NMR (400 MHz, CD_3OD) δ ppm 2.64 (d, *J*=6.6 Hz, 2 H) 3.01 (d, *J*=7.1 Hz, 2 H) 4.63 - 4.75 (m, 1 H) 7.05 (d, *J*=8.1 Hz, 1 H) 7.26 - 7.32 (m, 1 H) 7.35 (d, *J*=8.3 Hz, 2 H) 7.37 - 7.43 (m, 2 H) 7.44 (d, *J*=1.0 Hz, 1 H) 7.48 (dd, *J*=8.1, 1.77 Hz, 1 H) 7.52 - 7.60 (m, 4 H)

Example 5-60: 1H NMR (400 MHz, CD_3OD) δ ppm 2.30 - 2.44 (m, 2 H) 2.44 - 2.64 (m, 4 H) 2.87 (dd, *J*=13.7, 6.4 Hz, 1 H) 2.95 (dd, *J*=13.7, 6.4 Hz, 1 H) 4.42 - 4.53 (m, 1 H) 7.27 - 7.52 (m, 8 H)

Example 5-61: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 - 2.32 (m, 2 H) 2.32 - 2.44 (m, 4 H) 2.76 (d, *J*=6.6 Hz, 2 H) 4.16 - 4.29 (m, 1 H) 6.82 - 6.88 (m, 1 H) 6.89 - 6.97 (m, 1 H) 7.08 - 7.17 (m, 1 H) 7.17 - 7.28 (m, 3 H) 7.47 (d, *J*=8.1 Hz, 2 H) 7.90 (d, *J*=8.1 Hz, 1 H) 9.47 (br. s., 1 H) 12.14 (br. s., 1 H)

Example 5-62: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 - 2.31 (m, 2 H) 2.33 - 2.42 (m, 4 H) 2.72 - 2.85 (m, 2 H) 3.72 (s, 3 H) 4.16 - 4.34 (m, 1 H) 6.92 (ddd, *J*=9.4, 3.79, 1.8 Hz, 1 H) 7.21 - 7.33 (m, 4 H) 7.34 - 7.45 (m, 1 H) 7.92 (d, *J*=8.1 Hz, 1 H) 12.14 (br. s., 2 H)

Example 5-63: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.42 - 2.48 (m, 2 H) 2.85 (d, *J*=6.8 Hz, 2 H) 4.30 - 4.46 (m, 1 H) 6.99 (s, 1 H) 7.30 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.42 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.63 (d, *J*=8.1 Hz, 3 H) 7.67 - 7.77 (m, 2 H) 10.13 (br. s., 1 H) 10.22 (br. s., 1 H) 12.26 (br. s., 1 H)

Example 5-64: 1H NMR (400 MHz, CD_3OD) δ ppm 2.35 - 2.60 (m, 6 H) 2.85 (dd, *J*=13.7, 6.4 Hz, 1 H) 2.93 (dd, *J*=13.7, 6.4 Hz, 1 H) 3.65 (s, 3 H) 4.37 - 4.58 (m, 1 H) 7.05 - 7.18 (m, 3 H) 7.30 (d, *J*=8.1 Hz, 2 H) 7.44 (d, *J*=8.3 Hz, 2 H)

Example 5-65: 1H NMR (400 MHz, CD_3OD) δ ppm 2.38 - 2.56 (m, 6 H) 2.85 (dd, *J*=13.4, 7.3 Hz, 1 H) 2.89 (dd, *J*=13.4, 7.3 Hz, 1 H) 4.40 - 4.52 (m, 1 H) 7.26 - 7.35 (m, 3 H) 7.36 - 7.46 (m, 2 H) 7.52 - 7.61 (m, 3 H)

Example 5-66: 1H NMR (400 MHz, CD_3OD) δ ppm 2.31 - 2.58 (m, 6 H) 2.68 - 2.99 (m, 2 H) 3.63 (s, 3 H) 4.33 - 4.56 (m, 1 H) 6.92 - 7.18 (m, 3 H) 7.30 - 7.38 (m, 1 H) 7.38 - 7.46 (m, 2 H)

Example 5-67: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 - 2.65 (m, 2 H) 2.86 (dd, *J*=13.7, 8.1 Hz, 1 H) 2.95 (dd, *J*=13.7, 8.1 Hz, 1 H) 4.42 - 4.61 (m, 1 H) 6.89 - 6.99 (m, 1 H) 7.30 (d, *J*=8.3 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.42 - 7.51 (m, 1 H) 7.62 (d, *J*=8.1 Hz, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 7.76 (d, *J*=9.9 Hz, 1 H) 8.41 (d, *J*=9.1 Hz, 1 H) 12.26 (br. s., 1 H) 13.40 (s, 1 H)

Example 5-68: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 - 2.57 (m, 2 H) 2.90 (d, *J*=6.8 Hz, 2 H) 4.34 - 4.52 (m, 1 H) 7.15 (s, 1 H) 7.31 (d, *J*=8.1 Hz, 2 H) 7.39 (dd, *J*=7.6, 1.77 Hz, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.59 - 7.66 (m, 3 H) 7.70 (t, *J*=1.8 Hz, 1 H) 8.74 (d, *J*=8.6 Hz, 1 H)

Example 5-69: 1H NMR (400 MHz, CD3OD) δ ppm 2.61 (d, *J*=6.6 Hz, 2 H) 2.89 - 3.02 (m, 2 H) 4.53 - 4.71 (m, 1 H) 7.16 - 7.37 (m, 4 H) 7.39 (t, *J*=7.8 Hz, 1 H) 7.45 - 7.57 (m, 3 H) 7.59 (t, *J*=1.8 Hz, 1 H) 8.20 (d, 1 H).

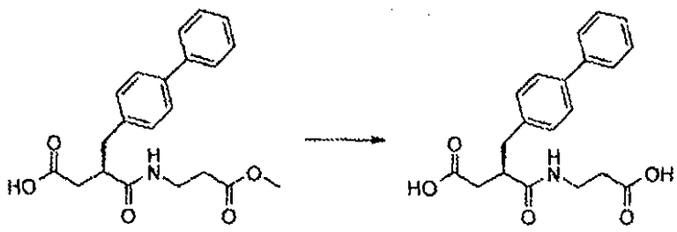
Example 5-70: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.41 - 2.57 (m, 2 H) 2.73 - 2.96 (m, 2 H) 4.35 - 4.46 (m, 1 H) 7.30 (d, *J*=8.3 Hz, 2 H) 7.35 - 7.44 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.57 - 7.67 (m, 4 H) 7.70 (t, *J*=1.9 Hz, 1 H) 8.23 (d, *J*=8.3 Hz, 1 H) 11.14 (s, 1 H) 12.29 (br. s., 1 H).

Example 5-71: 1H NMR (400 MHz, CD3OD) δ ppm 2.58 (dd, *J*=6.8, 1.8 Hz, 2 H) 2.95 (dd, *J*=7.0, 3.4 Hz, 2 H) 4.53 - 4.66 (m, 1 H) 7.27 - 7.36 (m, 3 H) 7.36-7.43 (m, 2H), 7.49-7.57 (m, 3H) 7.59 (t, *J*=1.7 Hz, 1 H).

Example 5-72: 1H NMR (400 MHz, CD3OD) δ ppm 2.60 - 2.71 (m, 2 H), 3.03 (dd, *J*=6.9, 4.7 Hz, 2 H), 3.28 (s, 3 H), 4.65 - 4.76 (m, 1 H), 7.06 (d, *J*=8.8 Hz, 1 H), 7.23 - 7.38 (m, 3 H), 7.38 - 7.47 (m, 2 H), 7.50 - 7.64 (m, 5 H), 8.03 (dd, *J*=8.8, 2.3 Hz, 1 H), 8.17 (d, 1 H), 8.56 (br. s., 1 H).

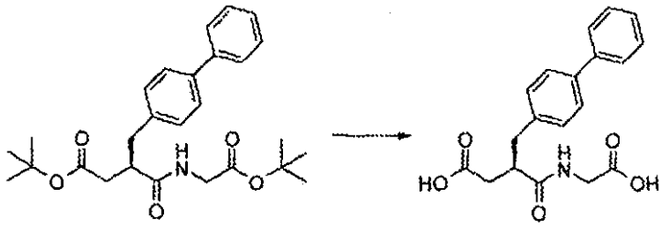
Example 5-73: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.43 - 2.59 (m, 2 H), 2.82 - 2.95 (m, 2 H), 4.04 - 4.16 (m, 1 H), 7.30 (d, J=8.3 Hz, 2 H), 7.34 (t, J=7.3 Hz, 1 H), 7.45 (t, J=7.6 Hz, 2 H), 7.59 (d, J=8.1 Hz, 3 H), 7.64 (d, J=8.6 Hz, 2 H), 8.03 (s, 1 H), 12.45 (br. s., 2 H).

Example 6-1: Synthesis of (*R*)-3-(biphenyl-4-ylmethyl)-4-(2-carboxyethylamino)-4-oxobutanoic acid



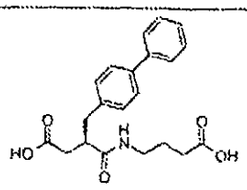
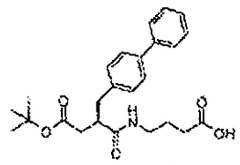
To a solution of (*R*)-3-(biphenyl-4-ylmethyl)-4-(3-methoxy-3-oxopropylamino)-4-oxobutanoic acid (22.1 mg, 0.060 mmol) in THF (0.6 mL) and methanol (0.1 mL), aqueous 1M NaOH (0.12 mL, 0.12 mmol) is added at room temperature. After stirring for 3 hours, additional aqueous 1M NaOH (0.12 mL, 0.12 mmol) is added. The reaction mixture is allowed to stir for 30 minutes and quenched with 0.5 mL of aqueous 1M HCl and 0.5 mL of brine. The mixture is extracted twice with ethyl acetate, and the organic layer is concentrated under reduced pressure to give (*R*)-3-(biphenyl-4-ylmethyl)-4-(2-carboxyethylamino)-4-oxobutanoic acid (16.4 mg). HPLC retention time = 1.04 minutes (condition A); MS (m+1) = 356.1; 1H NMR (400 MHz, DMSO-d6) δ ppm 2.13-2.31 (m, 3 H) 2.59 - 2.65 (m, 1 H) 2.81 - 2.90 (m, 2 H) 3.12 - 3.27 (m, 2 H) 7.26 (d, 2 H, J = 8 Hz) 7.34 (t, 1 H, J = 7.4 Hz) 7.45 (t, 2 H, J = 7.7 Hz) 7.57 (d, 2 H, J = 8.1 Hz) 7.63-7.65.

Example 7-1: Synthesis of (R)-3-biphenyl-4-ylmethyl-N-carboxymethyl-succinamic acid



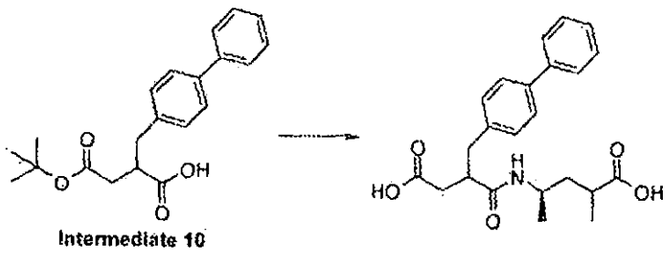
A solution of (R)-tert-butyl 3-(biphenyl-4-ylmethyl)-4-(2-tert-butoxy-2-oxoethylamino)-4-oxobutanoate (40 mg, 0.088 mmol) and TFA (0.5 mL, 6.49 mmol) in DCM (1.5 mL) is allowed to stir for 2 hours at room temperature. The reaction is concentrated under reduced pressure, and the obtained residue is suspended in DCM (0.5 mL) and heptane (2 mL), and collected on a funnel, giving (R)-3-biphenyl-4-ylmethyl-N-carboxymethyl-succinamic acid (9.6 mg). HPLC retention time = 1.26 minutes (condition A); MS (m+1) = 342.0; 1H NMR (400 MHz, CD3OD) δ ppm 2.39 (dd, J=16.67, 5.31 Hz, 1 H) 2.63 - 2.82 (m, 2 H) 2.98 - 3.14 (m, 2 H) 3.84 and 3.95 (AB, 2 H, J = 17.8 Hz) 7.26 - 7.33 (m, 3 H) 7.40 (t, J=7.71 Hz, 2 H) 7.56 (dd, J=19.96, 8.08 Hz, 4 H).

Following compounds are prepared using similar procedure as described in example 7-1:

Example #	Product	Starting Material	Hydrolysis Condition	HPLC-RT (condition)	MS (M+1)
Example 7-2	 (R)-3-biphenyl-4-ylmethyl-N-(3-carb oxy-propyl)-succinamic acid	 Intermediate 3	TFA, DCM, rt	1.35 min. (A)	370.0

Example 7-2: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.51-1.58 (m, 2 H) 2.12 - 2.21 (m, 3 H) 2.49- 2.65 (m, 2 H) 2.81 - 2.89 (m, 2 H) 2.94 - 3.08 (m, 2 H) 7.26 (d, 2 H, J = 8.1 Hz) 7.32 - 7.36 (m, 1 H) 7.43-7.46 (m, 2 H) 7.57 (d, 2 H, J = 8.0 Hz) 7.63-7.65 (m, 2H).

Example 8-1: Synthesis of (R)-4-(2-biphenyl-4-ylmethyl-3-carboxy-propionylamino)-2-methyl-pentanoic acid

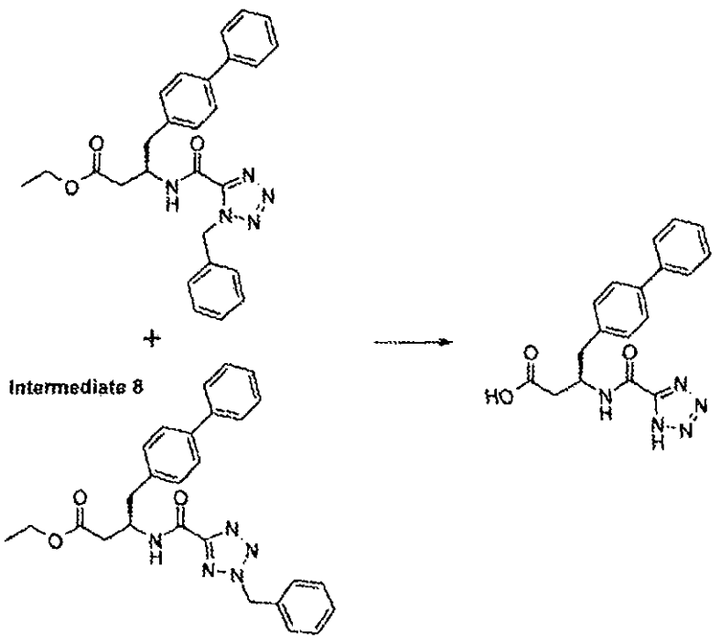


Intermediate 10

To a stirred solution of 2-biphenyl-4-ylmethyl-succinic acid 4-tert-butyl ester (100 mg, 0.29 mmol) in DMF (10 mL) is added HOBt (45 mg, 0.29 mmol) and EDCI (56 mg, 0.29 mmol) and the mixture is stirred at room temperature for 10 minutes then (2R,4R)-4-amino-2-methyl-pentanoic acid ethyl ester trifluoroacetate (47 mg, 0.29 mmol) and triethylamine (89 mg, 0.87 mmol) is added and the mixture is stirred at room temperature for 5 hours. The mixture is quenched with water and extracted with ethyl acetate. The organic layer is washed with water, brine, dried over magnesium sulfate and filtered. The solvent is removed under reduced pressure to give (2R,4R)-7-biphenyl-4-ylmethyl-2,4-dimethyl-6-oxo-nonanedioic acid 9-tert-butyl ester 1-ethyl ester.

Next, to a solution of (2R,4R)-7-biphenyl-4-ylmethyl-2,4-dimethyl-6-oxo-nonanedioic acid 9-tert-butyl ester 1-ethyl ester EtOH (4 mL) is added aqueous 1M NaOH (4 mL) and the mixture is stirred at room temperature for 30 minutes. The mixture is acidified to pH 2-3 with aqueous 1M HCl and is extracted with ethyl acetate. The solvent is removed under reduced pressure and the residue is purified by preparative HPLC using a gradient of 10-100% MeCN/water (0.1% TFA). Lyophilization of the proper fractions furnished (R)-4-(2-biphenyl-4-ylmethyl-3-carboxy-propionylamino)-2-methyl-pentanoic acid. HPLC retention time = 1.13 minutes (condition C); MS 398.2 (M+1); ^{1}H- NMR (400 MHz, DMSO-d6) δ ppm 0.93 (m, 6H), 1.23 (m, 1H), 1.59 (m, 1H), 2.17 (m, 1H), 2.63 (m, 1H), 2.82 (m, 1H), 3.72 (m, 1H), 7.27 (m, 2H), 7.33 (m, 1H), 7.45 (m, 2H), 7.56 (m, 2H), 7.62 (m, 2H), 7.71 (m, 1H), 12.07 (s, 1H).

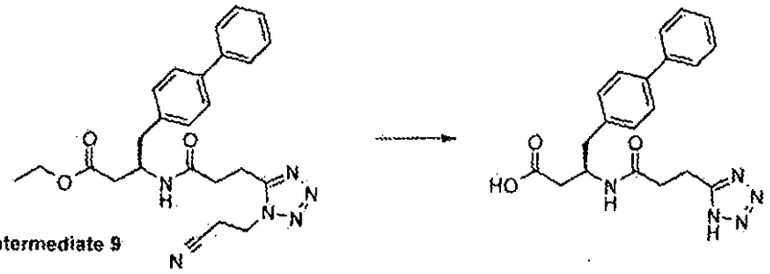
Example 9-1: Synthesis of (*R*)-4-biphenyl-4-yl-3-[(1*H*-tetrazole-5-carbonyl)-amino]-butyric acid



To a mixture of (R)-3-[(1-benzyl-1H-tetrazole-5-carbonyl)-amino]-4-biphenyl-4-yl-butyric acid ethyl ester and (R)-3-[(2-benzyl-2H-tetrazole-5-carbonyl)-amino]-4-biphenyl-4-yl-butyric acid ethyl ester (180 mg, 0.383 mmol) in EtOH (1 mL) and THF (1 mL) is added aqueous 1M LiOH (2 mL). After stirring for 0.5 hour, the reaction mixture is acidified with aqueous 1M HCl. The mixture is extracted with ethyl acetate, dried over Na_2SO_4, and concentrated under reduced pressure. The residue is dissolved in MeOH and hydrogenated with 10% Pd/C at room temperature for 3 hours and at 40°C for 2 hours. The reaction mixture is concentrated

and purified by reverse phase HPLC to give (*R*)-4-biphenyl-4-yl-3-[(1*H*-tetrazole-5-carbonyl)-amino]-butyric acid. HPLC retention time = 1.18 minutes (condition D); MS (m+1) = 352; ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.56 (dd, J=5.81, 15.92Hz, 1H), 2.67 (dd, J=7.58, 15.92Hz, 1H), 2.85-2.99 (m, 2H), 4.55-4.64 (m, 1H), 7.26-7.35 (m, 3H), 7.43 (dd, J=7.83, 7.83Hz, 2H), 7.56 (d, J=8.08Hz, 2H), 7.62 (d, J=7.07Hz, 2H), 9.28 (d, 8.84Hz, 1H), 12.28 (s, 1H).

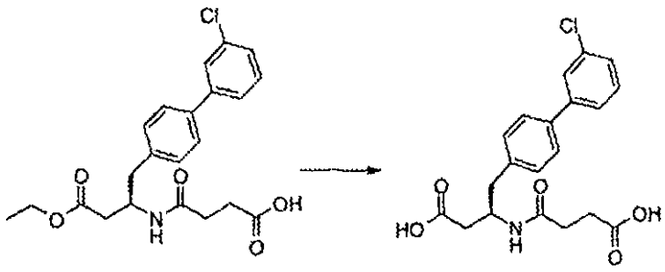
Example 10-1: (R)-4-bipheyl-4-yl-3-(3-1H-tetrazol-5-yl-propionylamino)-butyric acid



Intermediate 9

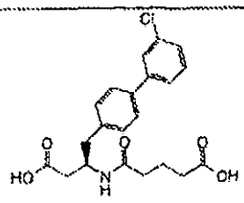
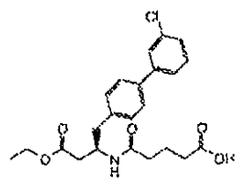
To a solution of (R)-4-biphenyl-4-yl-3-{3-[1-(2-cyano-ethyl)-1H-tetrazol-5-yl]-propionylamino}-butyric acid ethyl ester (137 mg, 0.297 mmol) in DCM (8 mL) at room temperature is added DBU (1.507 mL, 10.00 mmol) and the mixture is stirred at room temperature for 2 hours. The reaction is extracted with DCM. The combined organic layer is washed with saturated NH_4Cl, brine and dried over anhydrous sodium sulfate, filtered and concentrated under reduced. The obtained residue is purified by flash chromatography (silica gel, 2% to 10% EtOH/DCM) to give (R)-4-bipheyl-4-yl-3-(3-1H-tetrazol-5-yl-propionylamino)-butyric acid ethyl ester (37 mg). To the obtained ester in EtOH (2 mL) at room temperature is added aqueous 1M NaOH (1 mL, 1.0 mmol) and the mixture is stirred at room temperature for 1 hour. To the reaction is added 1 mL of aqueous 1M HCl to pH=4, and the mixture is purified by reverse phase HPLC [30% to 60% acetonitrile-H_2O (0.1% TFA)] to give (R)-4-bipheyl-4-yl-3-(3-1H-tetrazol-5-yl-propionylamino)-butyric acid. HPLC retention time = 1.24 minutes (condition C); MS (m+1) = 380; 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.37 (dd, *J*=6.7, 2.1 Hz, 2 H), 2.53 (t, *J*=7.6 Hz, 2 H), 2.69 - 2.82 (m, 2 H), 3.02 (t, *J*=7.7 Hz, 2 H), 4.17 - 4.29 (m, 1 H), 7.22 (d, *J*=8.3 Hz, 2 H), 7.34 (tt, *J*=7.3, 1.3 Hz, 1 H), 7.42 - 7.48 (m, 2 H), 7.57 (d, *J*=8.3 Hz, 2 H), 7.64 (dd, *J*=8.2, 1.1 Hz, 2 H), 8.00 (d, *J*=8.1 Hz, 1 H), 12.21 (br. s., 1 H), 15.92 (br. s., 1 H). Chiral HPLC retention time = 5.64 min. Column: Daicel CHIRALCEL OJ-H (4.6x100mm); flow rate = 1 ml/min.; eluent: EtOH(containing 0.1% TFA)/heptane = 2/8.

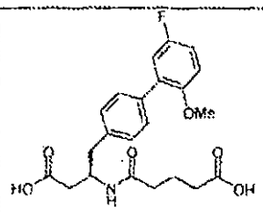
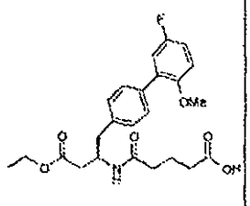
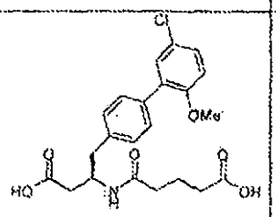
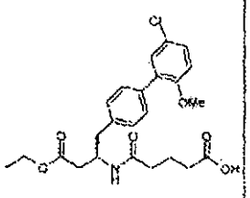
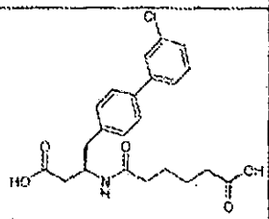
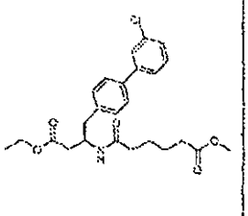
Example 11-1: Synthesis of (*R*)-4-(1-carboxy-3-(3'-chlorobiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid

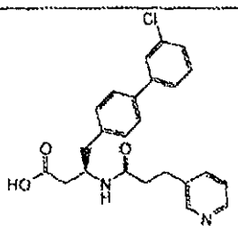
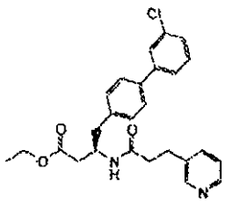
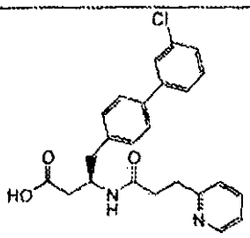
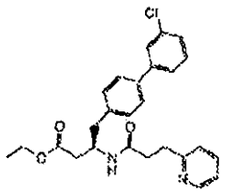
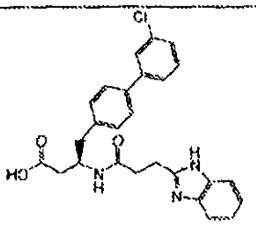
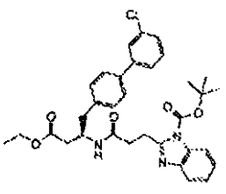


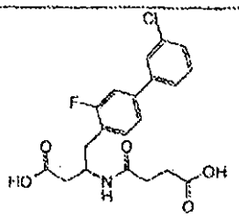
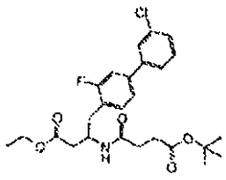
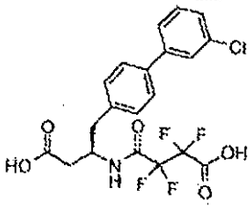
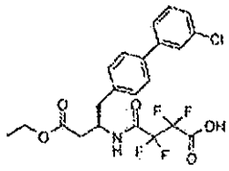
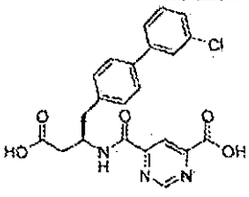
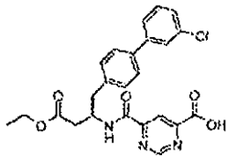
To a solution of (*R*)-4-(1-(biphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid (110 mg, 0.263 mmol) in THF (2 mL) and methanol (0.2 mL), aqueous 1M NaOH solution (1.053 mL, 1.053 mmol) is added at room temperature. After stirring for 1 hour, the reaction is quenched with 0.1 M aqueous HCl, and the solution is diluted with DCM (15 ml) and allowed to stir for 1.5 hours. The precipitated solid is collected on a funnel, washed with water, DCM, heptane and then DCM in that order, and dried under reduced pressure to (*R*)-4-(1-carboxy-3-(3'-chlorobiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid (66 mg). HPLC retention time = 0.87 minutes (condition B); MS (m+1) = 390.0; 1H NMR (400 MHz, CD_3OD) δ ppm 2.39-2.55 (m, 6 H) 2.86 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.6 Hz, 1 H) 2.92 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.2 Hz, 1 H) 4.42 - 4.49 (m, 1 H) 7.30 - 7.34 (m, 3 H) 7.40 (t, J = 7.4 Hz, 1 H) 7.51 - 7.56 (m, 3 H) 7.60 (t, J = 1.8 Hz, 1 H).

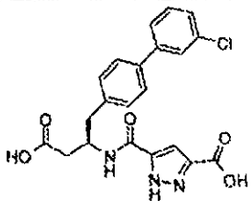
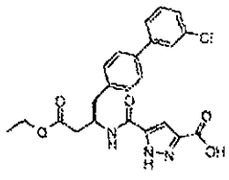
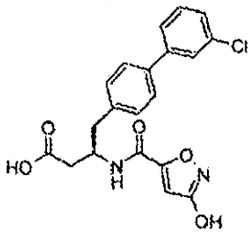
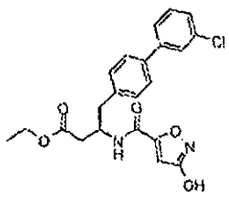
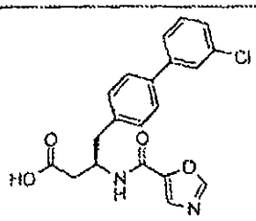
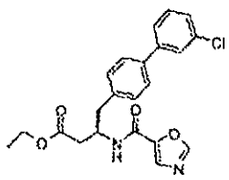
Following compounds are prepared using similar procedure as described in example 11-1:

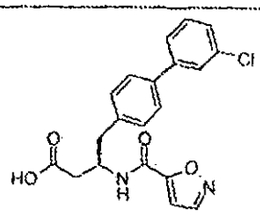
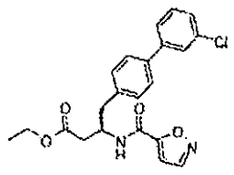
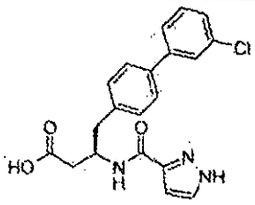
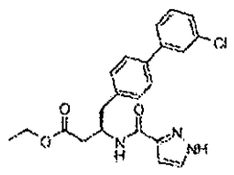
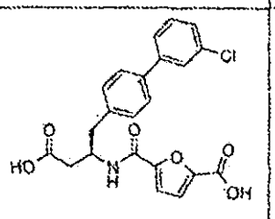
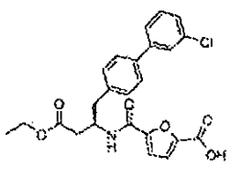
Example #	Product	Starting Material	Hydrolysis Condition	HPLC-RT (condition)	MS (M+1)
Example 11-2	 (R)-5-(1-carboxy-3-(3'-chlorobiphenyl-4-yl)propan-2-ylamino)-5-oxopentanoic acid		Aq. NaOH, THF, MeOH, RT	0.79 min. (B)	404.1

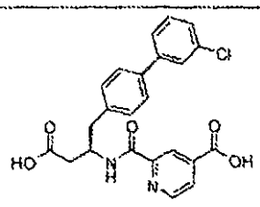
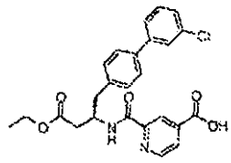
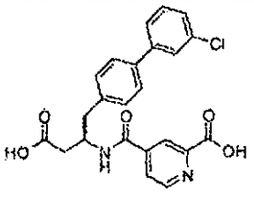
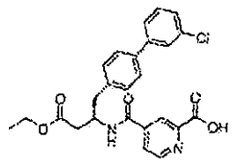
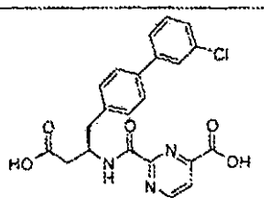
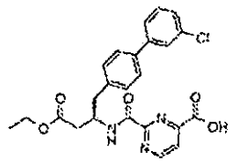
Example 11-3	 (R)-5-(1-carboxy-3-(5'-fluoro-2'-methoxybiphenyl-4-yl)propan-2-ylamino)-5-oxopentanoic acid		Aq. NaOH, THF, MeOH, RT	0.65 min. (B)	418.2
Example 11-4	 (R)-5-(1-carboxy-3-(5'-chloro-2'-methoxybiphenyl-4-yl)propan-2-ylamino)-5-oxopentanoic acid		Aq. NaOH, THF, MeOH, RT	0.63 min. (B)	434.3
Example 11-5	 (R)-6-(1-carboxy-3-(3'-chlorobiphenyl-4-yl)propan-2-ylamino)-6-oxohexanoic acid		Aq. NaOH, THF, MeOH, RT	1.40 min. (A)	418.3

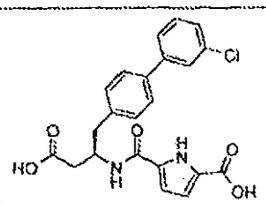
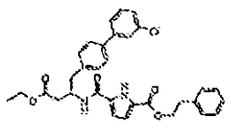
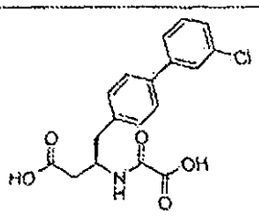
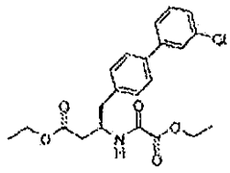
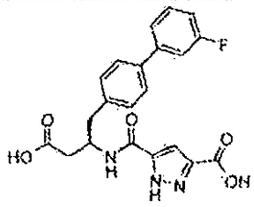
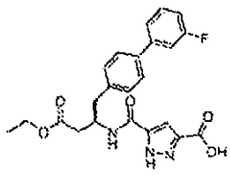
Example 11-6	 (R)-4-(3'-chlorobiphenyl-4-yl)-3-(3-(pyridin-3-yl)propanamido)butanoic acid		Aq. NaOH, THF, MeOH, RT	1.40 min. (A)	423.3
Example 11-7	 (R)-4-(3'-chlorobiphenyl-4-yl)-3-(3-(pyridin-2-yl)propanamido)butanoic acid		Aq. NaOH, THF, MeOH, RT	1.39 min. (A)	423.3
Example 11-9	 (R)-3-(3-(1H-benzo[d]imidazol-2-yl)propanamido)-4-(3'-chlorobiphenyl-4-yl)butanoic acid		Aq. NaOH, THF, MeOH, RT	1.50 min. (B)	462.3

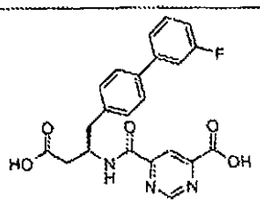
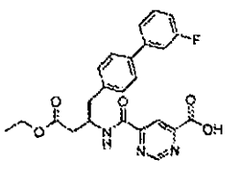
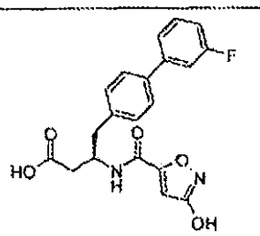
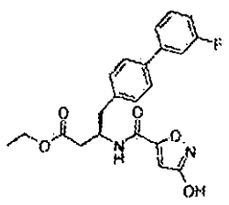
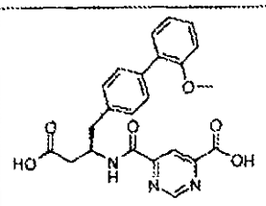
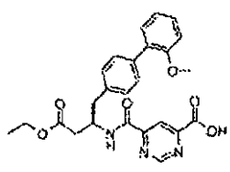
Example 11-10	 4-(1-carboxy-3-(3'-chloro-3-fluorobiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid		Aq. NaOH, THF, MeOH, 50 °C	0.72 min. (B)	408.2
Example 11-11	 N-[(R)-2-Carboxy-1-(3'-chloro-biphenyl-4-ylmethyl)-ethyl]-2,2,3,3-tetrafluoro-succinamic acid		Aq. NaOH, EtOH, rt	1.16 min. (C)	462.2
Example 11-12	 6-[(R)-2-Carboxy-1-(3'-chloro-biphenyl-4-ylmethyl)-ethylcarbamoyl]-pyrimidine-4-carboxylic acid		Aq. NaOH, EtOH, rt	1.34 min. (C)	440.2

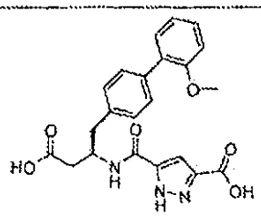
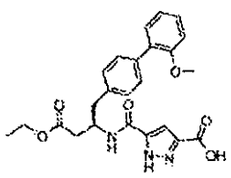
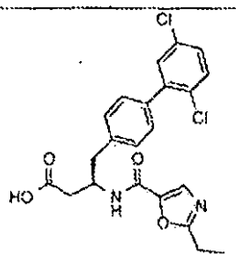
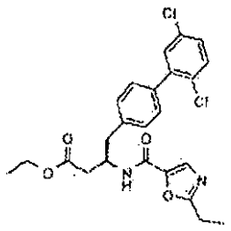
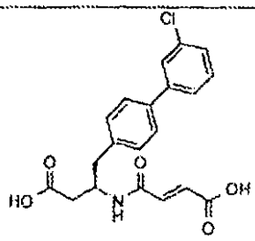
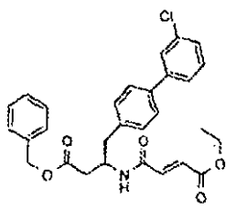
Example 11-13	 5-[(R)-2-Carboxy-1-(3'-chloro-biphenyl-4-ylmethyl)-ethylcarbamoyl]-1H-pyrazole-3-carboxylic acid		Aq. NaOH, EtOH, 50 °C	1.09 min. (C)	428.2
Example 11-14	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(3-hydroxy-isoxazole-5-carbonyl)-amino]-butyric acid		Aq. NaOH, EtOH, rt	1.17 min. (C)	401.0
Example 11-15	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(oxazole-5-carbonyl)-amino]-butyric acid		Aq. NaOH, EtOH, rt	1.12 min. (C)	385.2

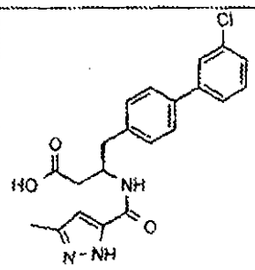
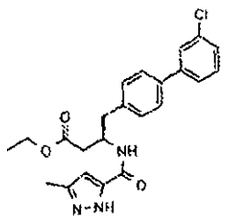
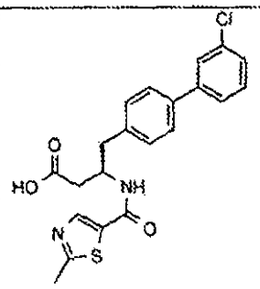
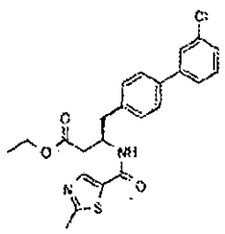
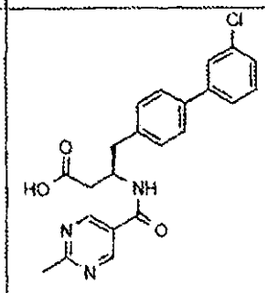
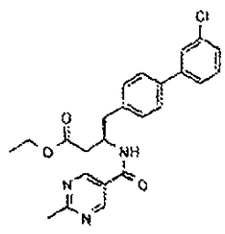
Example 11-16	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(isoxazole-5-carbonyl)-amino]-butyric acid		BCl_3, DCM, rt	1.15 min. (C)	385.1
Example 11-17	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(1H-pyrazole-3-carbonyl)-amino]-butyric acid		Aq. NaOH, EtOH, 50 °C	1.18 min. (C)	384.3
Example 11-18	 5-[(R)-2-Carboxy-1-(3'-chloro-biphenyl-4-ylmethyl)-ethylcarbamoyl]-furan-2-carboxylic acid		Aq. NaOH, EtOH, 50 °C	1.08 min. (C)	428.2

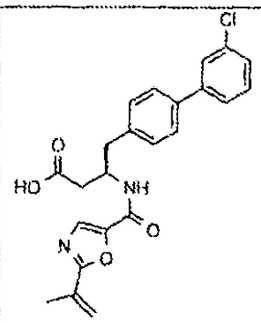
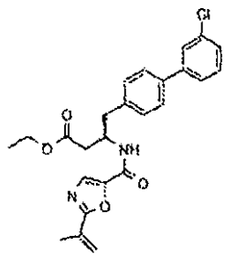
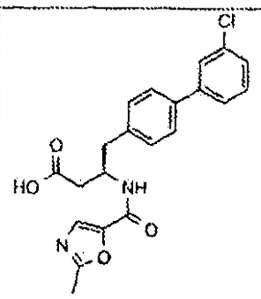
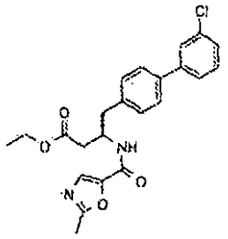
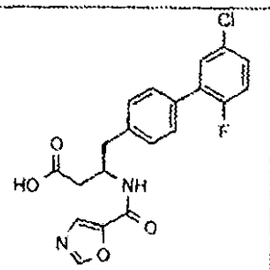
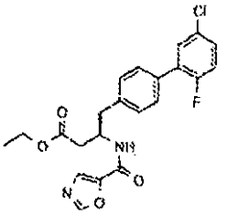
Example 11-19	 2-[(R)-2-Carboxy-1-(3'-chloro-biphenyl-4-ylmethyl)-ethylcarbamoyl]-isonicotinic acid		Aq. NaOH, EtOH, rt	1.04 min. (C)	439.3
Example 11-20	 4-[(R)-2-Carboxy-1-(3'-chloro-biphenyl-4-ylmethyl)-ethylcarbamoyl]-pyridine-2-carboxylic acid		Aq. NaOH, EtOH, rt	1.03 min. (C)	439.2
Example 11-21	 2-[(R)-2-Carboxy-1-(3'-chloro-biphenyl-4-ylmethyl)-ethylcarbamoyl]-pyrimidine-4-carboxylic acid		Aq. NaOH, EtOH, rt	0.89 min. (C)	440.1

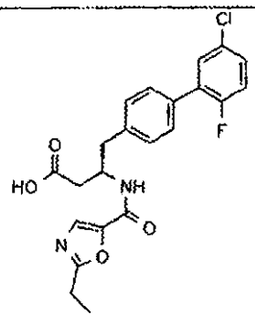
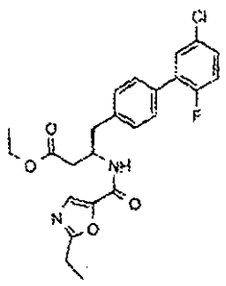
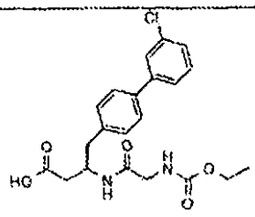
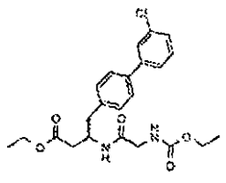
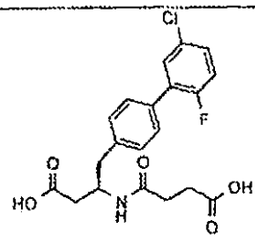
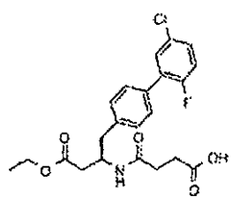
Example 11-22	 5-[(R)-2-Carboxy-1-(3'-chloro-biphenyl-4-ylmethyl)-ethylcarbamoyl]-1H-pyrrole-2-carboxylic acid		Aq. NaOH, EtOH, rt	1.09 min. (C)	427.3
Example 11-23	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-(oxalyl-amino)-butyric acid		Aq. NaOH, EtOH, rt	0.9 min. (C)	362.1
Example 11-24	 5-[(R)-2-Carboxy-1-(3'-fluoro-biphenyl-4-ylmethyl)-ethylcarbamoyl]-1H-pyrazole-3-carboxylic acid		Aq. NaOH, EtOH, 50 °C	0.96 min. (C)	412.1

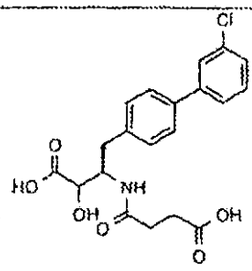
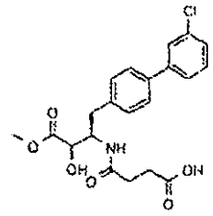
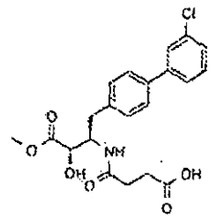
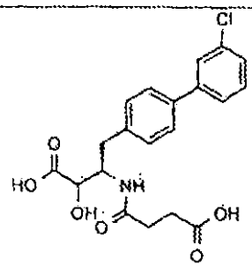
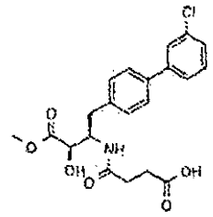
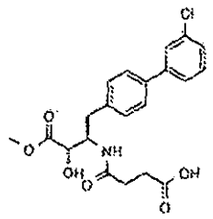
Example 11-25	 6-[(R)-2-Carboxy-1-(3'-fluoro-biphenyl-4-ylmethyl)-ethylcarbamoyl]-pyrimidine-4-carboxylic acid		Aq. NaOH, EtOH, rt	0.97 min. (C)	424.4
Example 11-26	 (R)-4-(3'-Fluoro-biphenyl-4-yl)-3-[(3-hydroxy-isoxazole-5-carbonyl)-amino]-butyric acid		Aq. NaOH, EtOH, rt	0.83 min. (C)	385.1
Example 11-27	 6-[(R)-2-Carboxy-1-(2'-methoxy-biphenyl-4-ylmethyl)-ethylcarbamoyl]-pyrimidine-4-carboxylic acid		Aq. NaOH, EtOH, rt	1.22 min. (C)	436.2

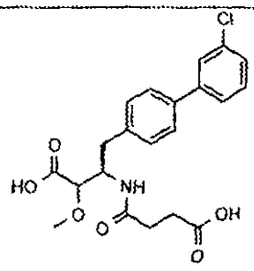
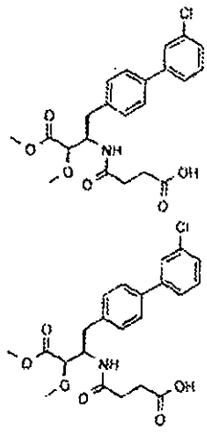
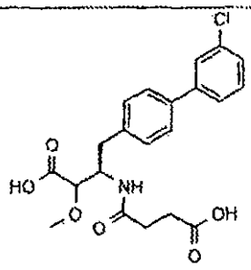
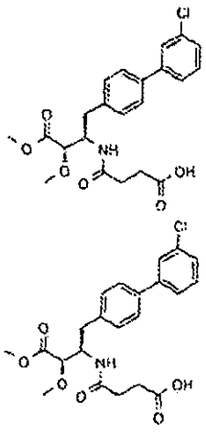
Example 11-28	 5-[(R)-2-Carboxy-1-(2'-methoxy-biphenyl-4-ylmethyl)-ethylcarbamoyl]-1H-pyrazole-3-carboxylic acid		Aq. NaOH, EtOH, 50 °C	0.98 min. (C)	424.0
Example 11-29	 (R)-4-(2',5'-Dichloro-biphenyl-4-yl)-3-[(2-ethyl-oxazole-5-carbonyl)-amino]-butyric acid		Aq. NaOH, MeOH, rt	1.52 min. (D)	448.1
Example 11-30	 (E)-3-[(R)-2-Carboxy-1-(3'-chloro-biphenyl-4-ylmethyl)-ethylcarbamoyl]-acrylic acid		Aq. NaOH, THF, MeOH, rt	1.12 min. (A)	388.3

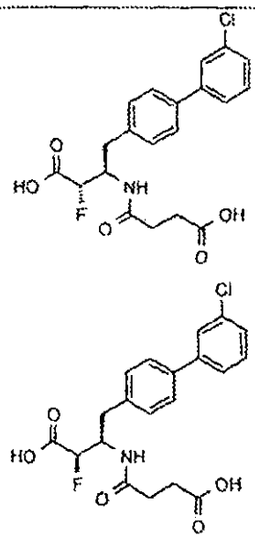
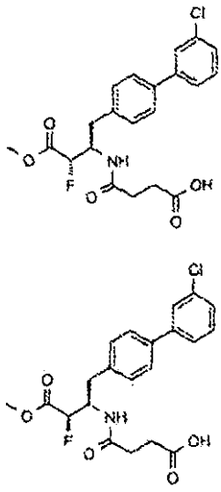
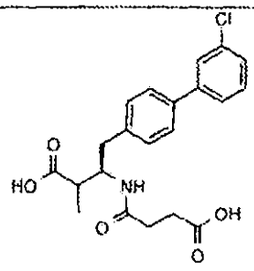
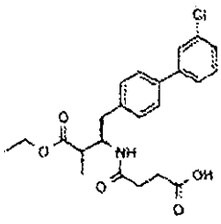
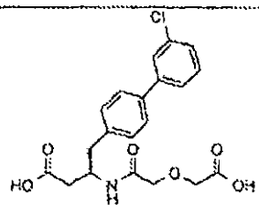
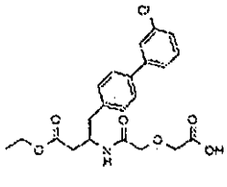
Example 11-31	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(5-methyl-2H-pyrazole-3-carbonyl)-amino]-butyric acid		Aq. NaOH, MeOH, rt	1.52 min. (D)	398.1
Example 11-32	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(2-methyl-thiazole-5-carbonyl)-amino]-butyric acid		Aq. NaOH, MeOH, rt	1.56 min. (D)	415.0
Example 11-33	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(2-methyl-pyrimidine-5-carbonyl)-amino]-butyric acid		Aq. NaOH, MeOH, rt	1.56 min. (D)	410.1

Example 11-34	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(2-isopropenyl-oxazole-5-carbonyl)-amino]-butyric acid		Aq. NaOH, MeOH, rt	1.75 min. (D)	425.1
Example 11-35	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(2-methyl-oxazole-5-carbonyl)-amino]-butyric acid		Aq. NaOH, MeOH, rt	1.63 min. (D)	399.1
Example 11-36	 (R)-4-(5'-Chloro-2'-fluoro-biphenyl-4-yl)-3-[(oxazole-5-carbonyl)-amino]-		Aq. NaOH, MeOH, rt	1.62 min. (D)	403.0

	butyric acid				
Example 11-37	 (R)-4-(5'-Chloro-2'-fluoro-biphenyl-4-yl)-3-[(2-ethyl-oxazole-5-carbonyl)-amino]-butyric acid		Aq. NaOH, MeOH, rt	1.73 min. (D)	431.1
Example 11-38	 (R)-4-(3'-Chloro-biphenyl-4-yl)-3-(2-ethoxycarbonylamino-acetylamino)-butyric acid		Aq. NaOH, THF, MeOH, rt	0.80 min. (B)	419.2
Example 11-39	 (R)-3-(3-Carboxy-propionylamino)-4-		Aq. NaOH, THF, MeOH, rt	0.66 min. (B)	408.1

	(5'-chloro-2'-fluoro-biphenyl-4-yl)-butyric acid				
Example 11-40	 (major product) (R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-hydroxy-butyric acid	 	Aq. NaOH, MeOH, rt	1.07 min. (A)	406.0
Example 11-41	 (minor product) (R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-hydroxy-butyric acid	 	Aq. NaOH, MeOH, rt	1.04 min. (A)	406.0

Example 11-42	 (major product) (R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-methoxy-butyric acid		Aq. NaOH, MeOH, rt	*0.97 min.* (A)	420.1
Example 11-43	 (*minor* product) (R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-methoxy-butyric acid		Aq. NaOH, MeOH, rt	0.96 min. (A)	420.1

Example 11-44	 (R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-fluoro-butyric acid		Aq. NaOH, MeOH, rt	1.07 min (A)	408.1
Example 11-45	 (R)-3-(3-Carboxy-propionylamino)-4-(3'-chloro-biphenyl-4-yl)-2-methyl-butyric acid		Aq. NaOH, MeOH, rt	0.53 min. (B)	404
Example 11-46			Aq. NaOH, MeOH, rt	0.37 min. (B)	406

	(R)-3-(2-Carboxymethoxy-acetylamino)-4-(3'-chloro-biphenyl-4-yl)-butyric acid				

Example 11-2: 1H NMR (400 MHz, CD_3OD) δ ppm 1.76 - 1.83 (m, 2 H) 2.15 - 2.21 (m, 4 H) 2.49 (A of ABX, J_{ab} = 15.7 Hz, J_{ax} = 7.3 Hz, 1 H) 2.53 (B of ABX, J_{ab} = 15.7 Hz, J_{bx} = 6.1 Hz, 1 H) 2.83 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.3 Hz, 1 H) 2.93 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 5.8 Hz, 1 H) 4.46 – 4.53 (m, 1 H) 7.30 – 7.33 (m, 3 H) 7.39 (t,, J = 7.8 Hz, 1 H) 7.51 - 7.55 (m, 3 H) 7.59 – 7.60 (m, 1 H).

Example 11-3: 1H NMR (400 MHz, CD_3OD) δ ppm 1.77 - 1.84 (m, 2 H) 2.16 - 2.23 (m ,4 H) 2.39 - 2.42 (m, 2 H) 2.49 (A of ABX, J_{ab} = 15.6 Hz, J_{ax} = 7.5 Hz, 1 H) 2.53 (B of ABX, J_{ab} = 15.6 Hz, J_{bx} = 6.1 Hz, 1 H) 2.83 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 6.1 Hz, 1 H) 2.91 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.3 Hz, 1 H) 3.75 (s, 3 H) 4.46 – 4.53 (m, 1 H) 6.97 - 7.04 (m, 2 H) 7.26 (d, J = 8.1 Hz, 2 H) 7.42 (d, J = 8.1 Hz, 2 H).

Example 11-4: 1H NMR (400 MHz, CD_3OD) δ ppm 1.77 - 1.84 (m, 2 H) 2.16 - 2.24 (m, 4 H) 2.49 (A of ABX, J_{ab} = 15.6 Hz, J_{ax} = 7.5 Hz, 1 H) 2.54 (B of ABX, J_{ab} = 15.6 Hz, J_{bx} = 6.1 Hz, 1 H) 2.83 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.2 Hz, 1 H) 2.91 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.1 Hz, 1 H) 3.77 (s, 3 H) 4.45 – 4.52 (m, 1 H) 7.03 (d, J = 8.6 Hz, 1 H) 7.24 – 7.28 (m, 3 H) 7.39 - 7.41 (m, 2 H).

Example 11-5: 1H NMR (400 MHz, CD_3OD) δ ppm 1.49 - 1.56 (m, 4 H) 2.13 (t, J = 6.8 Hz, 2 H) 2.23 (t, J = 6.9 Hz, 2 H) 2.45 - 2.56 (m, 2 H) 2.80 - 2.86 (m, 1 H) 2.91 - 2.96 (m, 1 H) 4.46 - 4.53 (m, 1 H) 7.31 - 7.33 (m, 3 H) 7.40 (t, J = 8.0 Hz, 1 H) 7.52 - 7.55 (m, 3 H) 7.59 (br t, J = 1.8 Hz, 1 H).

Example 11-6: 1H NMR (400 MHz, CD_3OD) δ ppm 2.39 - 2.57 (m, 4 H) 2.80 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.1 Hz, 1 H) 2.89 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.1 Hz, 1 H) 3.04 (t, J = 7.1 Hz, 2 H) 3.75 (s, 3 H) 4.40 – 4.47 (m, 1 H) 7.27 - 7.29 (m ,2 H) 7.32 - 7.35 (m, 1 H) 7.41 (t, J = 7.8 Hz, 1 H) 7.51 - 7.54 (m, 3 H) 7.59 - 7.60 (m, 1 H) 7.83 - 7.84 (m, 1 H) 8.28 (br d, J = 7.1 Hz, 1 H) 8.55 (d, J = 5.6 Hz, 1 H) 8.62 (s, 1 H).

Example 11-7: 1H NMR (400 MHz, CD_3OD) δ ppm 2.47 (A of ABX, J_{ab} = 15.7 Hz, J_{ax} = 7.7 HZ, 1 H) 2.54 (B of ABX, J_{ab} = 15.7 Hz, Jbx = 5.8 Hz, 1 H) 2.64 - 2.75 (m, 2 H) 2.80 (A of ABX, J_{ab} = 13.7 Hz, J_{ax} = 8.3 Hz, 1 H) 2.92 (B of ABX, J_{ab} = 13.7 Hz, J_{bx} = 5.9 Hz, 1 H) 3.17 - 3.21 (m, 2 H) 4.43 – 4.50 (m, 1 H) 7.28 - 7.35 (m, 3 H) 7.39 - 7.43 (m, 1 H) 7.51 - 7.54 (m, 3 H) 7.59 (br t, *J* = 1.9 Hz, 1 H) 7.69 - 7.75 (m, 2 H) 8.29 - 8.32 (m, 1 H) 8.61 (d, *J* = 4.6 Hz, 1 H).

Example 11-8: 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.82 - 1.89 (m, 2 H) 2.29 (t, *J* = 7.3 Hz, 2 H) 2.56 (A of ABX, J_{ab} = 16.4 Hz, J_{ax} = 5.6 Hz, 1 H) 2.64 (B of ABX, J_{ab} = 16.4 Hz, J_{bx} = 5.1 Hz, 1 H) 2.95 (A of ABX, J_{ab} = 13.8 Hz, J_{ax} = 7.6 Hz, 1 H) 2.99 (B of ABX, J_{ab} = 13.8 Hz, J_{bx} = 7.2 Hz, 1 H) 3.30 (s, 3 H) 3.38 (t, *J* = 5.9 Hz, 2 H) 4.10 (q, *J* = 7.1 Hz, 2 H) 4.52 – 4.57 (m, 1 H) 6.59 (br d, *J* = 8.6 Hz, 1 H) 7.26 - 7.37 (m, 4 H) 7.42 - 7.45 (m, 1 H) 7.48 - 7.52 (m, 2 H) 7.55 (br t, *J* = 1.6 Hz, 1 H).

Example 11-9: 1H NMR (400 MHz, CD_3CN+D_2O) δ ppm 2.43 - 2.56 (m, 2 H) 2.71 - 2.91 (m, 4 H) 3.21 - 3.34 (m, 2 H) 4.39 - 4.46 (m, 1 H) 7.27 (d, *J* = 8.3 Hz, 2 H) 7.34 - 7.49 (m, 7 H) 7.55 - 7.56 (m, 1 H) 7.65 - 7.70 (m, 2 H).

Example 11-10: 1H NMR (400 MHz, CD_3OD) δ ppm 2.38 - 2.41 (m, 2 H) 2.47 - 2.58 (m, 4 H) 2.85 – 2.90 (m, 1 H) 2.99 – 3.04 (m, 1 H) 4.48 – 4.55 (m, 1 H) 7.32 - 7.44 (m, 5 H) 7.53 - 7.56 (m, 1 H) 7.62 - 7.63 (m, 1 H).

Example 11-11: 1H NMR (400 MHz, DMSO-d6): 1H NMR (400 MHz, DMSO-d6): δ ppm 2.44-2.52 (m, 2H), 2.83-2.85 (d, J=6.82 Hz, 2H), 4.29-4.38 (m, 1H), 7.28-7.30 (d, J=8.34 Hz, 2H), 7.40-7.43 (t, J=7.83 Hz, 1H), 7.62-7.65 (m, 3H), 7.71-7.72 (t, J=1.77 Hz, 1H), 9.42-9.45 (M, 1H), 12.32 (s, 1H).

Example 11-12: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.54-2.59 (m, 1H), 2.64-2.70 (m, 1H), 2.88-2.93 (m, 1H), 2.98-3.03 (m, 1H), 4.56-4.63 (m, 1H), 7.30-7.32 (m, 2H), 7.37-7.40 (m, 1H), 7.43-7.47 (t, J=7.83 Hz, 1H), 7.59-7.61 (m, 3H), 7.67-7.68 (t, J=2.02 Hz, 1H), 8.32 (d, J=1.26 Hz, 1H), 9.17-9.19 (d, J=9.09 Hz, 1H), 9.50 (d, J=1.52 Hz, 1H), 12.34 (s, 1H), 14.14 (s, 1H).

Example 11-13: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.46-2.60 (m, 2H), 2.84-2.96 (m, 2H), 4.51 (m, 1H), 7.31 (d, J=8.34 Hz, 2H), 7.38-7.41 (m, 1H), 7.46 (t, 1H), 7.62 (d, J=8.34 Hz, 3H), 7.69 (t, 1H).

Example 11-14: 1H NMR (400 MHz, DMSO-d6) δ ppm) 2.75 - 2.99 (m, 1 H) 4.47 (d, J=7.58 Hz, 1 H) 6.49 (s, 1 H) 7.30 (d, J=8.34 Hz, 1 H) 7.37 - 7.43 (m, 1 H) 7.47 (t, J=7.83 Hz, 1 H) 7.63 (d, J=8.08 Hz, 2 H) 7.70 (t, J=1.77 Hz, 1 H) 8.80 (d, J=8.59 Hz, 1 H) 11.69 (s, 1 H) 12.04 - 12.58 (m, 1 H).

Example 11-15: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.81 - 2.96 (m, 2 H) 4.42 - 4.55 (m, 1 H) 7.31 (d, J=8.34 Hz, 2 H) 7.36 - 7.43 (m, 1 H) 7.47 (t, J=7.83 Hz, 1 H) 7.63 (d, J=8.34 Hz, 4 H) 7.69 (t, J=1.77 Hz, 1 H) 7.72 (s, 1 H) 8.54 (s, 1 H) 8.60 (d, J=8.59 Hz, 1 H) 12.29 (br. s., 1 H).

Example 11-16: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.53 - 2.64 (m, 2 H) 2.84 - 2.93 (m, 2 H) 4.41 - 4.59 (m, 1 H) 7.00 (d, J=2.02 Hz, 1 H) 7.31 (d, J=8.08 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 (t, J=7.83 Hz, 1 H) 7.58 - 7.65 (m, 3 H) 7.70 (t, J=1.77 Hz, 1 H) 8.72 (d, J=1.77 Hz, 1 H) 8.95 (d, J=8.59 Hz, 1 H) 12.31 (br. s., 1 H).

Example 11-17: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.46-2.60 (m, 2H), 2.83-2.98 (m, 2H), 4.52 (m, 1H), 6.61 (d, J=2.27 Hz, 1H), 7.31 (d, J=8.34 Hz, 2H), 7.37-7.42 (m, 1H), 7.46 (t, 1H), 7.62 (d, J=8.34 Hz, 3H), 7.69 (t, 1H), 7.74 (d, J=2.02 Hz, 1H), 8.13 (d, J=8.84 Hz, 1H).

Example 11-18: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.48-2.62 (m, 2H), 2.84-2.96 (m, 2H), 4.52 (m, 1H), 7.16 (d, J=3.54 Hz, 1H), 7.27 (d, J=3.79 Hz, 1H), 7.31 (d, J=8.34 Hz, 2H), 7.38-7.41 (m, 1H), 7.47 (t, 1H), 7.63 (d, J=8.34 Hz, 3H), 7.70 (t, 1H), 8.59 (d, J=8.59 Hz, 1H).

Example 11-19: 1H NMR (400 MHz, DMSO-d6): 1H NMR (400 MHz, DMSO-d6): δ ppm 2.54-2.67 (m, 2H), 2.88-2.92 (m, 1H), 2.99-3.05 (m, 1H), 4.53-4.62 (m, 1H), 7.31-7.33 (m, 2H), 7.37-7.39 (m, 1H), 7.43-7.47 (t, J = 7.58 Hz, 1H), 7.60-7.62 (m, 3H), 7.68 (m, 1H), 7.86-7.87 (d, J=4.55 Hz, 1H), 8.30 (s, 1H), 8.62-8.63 (d, J=4.80 Hz, 1H), 8.80-8.83 (d, J=9.09 Hz, 1H).

Example 11-20: 1H NMR (400 MHz, DMSO-d6): 1H NMR (400 MHz, DMSO-d6): δ ppm 2.50-2.53 (m, 1H), 2.56-2.59 (t, J=6.32 Hz, 1H), 2.90-2.98 (m, 2H), 4.51-4.58 (m, 1H), 7.33-7.35 (d, J=8.34 Hz, 2H), 7.39-7.42 (m, 1H), 7.45-7.49 (t, J=7.83 Hz, 1H), 7.61-7.65 (m, 3H), 7.69-7.70 (t, J=1.77 Hz, 1H), 7.90-7.91 (dd, J=1.77 Hz, 5.05 Hz, 1H), 8.38-8.39 (m, 1H), 8.83-8.85 (dd, J=0.76 Hz, 5.05 Hz, 1H), 8.91-8.93 (d, J=8.34 Hz, 1H).

Example 11-21: 1H NMR (400 MHz, DMSO-d6): 1H NMR (400 MHz, DMSO-d6): δ ppm 2.45-2.55 (m, 1H), 2.59-2.67 (m, 1H), 2.88-2.93 (m, 1H), 2.99-3.05 (m, 1H), 4.51-4.61 (m, 1H), 7.32-7.34 (d, J=8.08 Hz, 2H), 7.37-7.40 (m, 1H), 7.44-7.48 (t, J=7.58 Hz, 1H), 7.60-7.62 (t, J=7.83 Hz, 2H), 7.69 (s, 1H), 7.77 (s, 1H), 8.86-8.87 (d, J=4.04 Hz, 1H), 9.06 (s, 1H).

Example 11-22: 1H NMR (400 MHz, DMSO-d6): δ ppm 2.49-2.53 (m, 2H), 2.90-2.92 (d, J=6.82 Hz, 2H), 4.42-4.51 (m, 1H), 6.72-6.73 (d, J=2.27 Hz, 2H), 7.32-7.34 (m, 2H), 7.39-7.42 (m, 1H), 7.45-7.49 (t, J = 7.83 Hz, 1H), 7.62-7.66 (m, 3H), 7.70-7.71 (t, J=1.77 Hz, 1H), 8.27-8.29 (d, J=8.08 Hz, 1H), 11.96 (s, 1H), 12.33 (s, 1H), 12.75 (s, 1H).

Example 11-23: 1H NMR (400 MHz, DMSO-d6): 1H NMR (400 MHz, DMSO-d6): δ ppm 2.44-2.55 (m, 2H), 2.79-2.89 (m, 2H), 4.29-4.38 (m, 1H), 7.27-7.29 (d, J=8.08 Hz, 2H), 7.39-7.42 (m, 1H), 7.45-7.49 (t, J=8.08 Hz, 1H), 7.62-7.64 (d, J=8.08 Hz, 3H), 7.70-7.71 (m, 1H), 8.85-8.87 (d, J=9.09 Hz, 1H), 12.30 (s, 1H).

Example 11-24: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.46-2.60 (m, 2H), 2.84-2.96 (m, 2H), 4.51 (m, 1H), 7.15 (m, 2H), 7.44-7.52 (m, 3H), 7.62 (d, J=8.34 Hz, 2H), 8.38 (d, broad, J=7.58 Hz, 1H).

Example 11-25: 1H NMR (400 MHz, DMSO-d6): δ ppm 2.54-2.59 (m, 1H), 2.64-2.70 (m, 1H), 2.88-2.93 (m, 1H), 2.98-3.03 (m, 1H), 4.56-4.65 (m, 1H), 7.13-7.18 (m, 1 H), 7.30-7.32 (d, J=8.34 Hz, 2H), 7.45-7.48 (m, 3H), 7.60-7.62 (d, J=8.34 Hz, 2H), 8.31-8.32 (d, J=1.26 Hz, 1H), 8.17-8.19 (d, J=9.09 Hz, 1H), 8.49 (d, J=1.26 Hz, 1H), 12.32 (s, 1H), 14.10 (s, 1H).

Example 11-26: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.52 - 2.62 (m, 2 H) 2.83 - 2.92 (m, 2 H) 4.47 (d, J=7.07 Hz, 1 H) 6.49 (s, 1 H) 7.11 - 7.21 (m, 1 H) 7.30 (d, J=8.34 Hz, 2 H) 7.42 - 7.55 (m, 3 H) 7.64 (d, J=8.34 Hz, 2 H) 8.80 (d, J=8.59 Hz, 1 H) 11.68 (br. s., 1 H) 12.30 (br. s., 1 H).

Example 11-27: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.51-2.57 (m, 1H), 2.64-2.70 (m, 1H), 2.84-2.89 (dd, J=6.06 Hz, 1H), 2.96-3.01 (dd, J=7.83 Hz, 1H), 3.72 (s, 3H), 4.54-4.63 (m, 1H), 6.96-7.00 (m, 1H), 7.06-7.08 (dd, J=0.76 Hz, 1H), 7.22-7.24 (m, 3H), 7.28-7.32 (m, 1H), 7.35-7.38 (m, 2H), 8.33-8.34 (d, J=1.26 Hz, 1H), 9.16-9.18 (d, J=9.09 Hz, 1H), 9.49 (d, J=1.52 Hz, 1H), 12.31 (s, 1H), 14.13 (s, 1H).

Example 11-28: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.52-2.60 (m, 2H), 2.73 (s, 1H), 2.89 (s, 1H), 2.81-2.95 (m, 2H), 3.74 (s, 3H), 4.50 (m, 1H), 7.00 (t, 1H), 7.08 (d, J=8.34 Hz, 1H), 7.15 (s, broad, 1H), 7.23-7.26 (m, 3H), 7.29-7.33 (m, 1H), 7.38 (d, J=8.08 Hz, 2H), 8.39 (d, broad, J=7.07 Hz, 1H).

Example 11-29: 1H NMR (400 MHz, CD_3OD) δ ppm 1.33 (t, *J*=7.6 Hz, 3 H) 2.66 (d, *J*=6.8 Hz, 2 H) 2.84 (q, *J*=7.6 Hz, 2 H) 2.98 (dd, *J*=13.6, 8.1 Hz, 1 H) 3.03 (dd, *J*=13.6, 6.6 Hz, 1 H) 4.64 - 4.76 (m, 1 H) 7.24 - 7.37 (m, 6 H) 7.40 - 7.45 (m, 1 H) 7.53 (s, 1 H).

Example 11-30: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.40 – 2.51 (m, 2 H) 2.79 – 2.90 (m, 2 H) 4.29 – 4.38 (m, 1 H) 6.47 (d, *J* = 15.7 Hz, 1 H) 6.88 (d, *J* = 15.7 Hz 1 H) 7.28 – 7.30 (m, 2 H) 7.39 – 7.41 (m, 1 H) 7.47 (t, *J* = 8.0 Hz, 1 H) 7.62 – 7.65 (m, 2 H) 7.70 – 7.71 (m, 1 H) 8.54 (d, *J* = 8.1 Hz, 1 H) 7.31 (d, *J* = 8.3 HZ, 2 H) 7.40 – 7.43 (m, 1 H) 7.47 – 7.50 (m, 1 H) 7.62 – 7.65 (m, 3 H) 7.69 – 7.71 (m, 1 H) 8.54 (d, J = 8.1 Hz, 1 H)

Example 11-31: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H) 2.43 - 2.49 (m, 1 H) 2.52 - 2.60 (m, 1 H) 2.84 (dd, *J*=13.6, 6.1 Hz, 1 H) 2.94 (dd, *J*=13.6, 8.1 Hz, 1 H) 4.39 - 4.58 (m, 1 H) 6.33 (s, 1 H) 7.30 (d, *J*=8.3 Hz, 2 H) 7.36 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.61 (d, *J*=8.3 Hz, 3 H) 7.69 (t, *J*=1.9 Hz, 1 H) 8.02 (d, *J*=7.8 Hz, 1 H).

Example 11-32: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 - 2.56 (m, 2 H) 2.89 (d, *J*=6.8 Hz, 2 H) 3.31 (s, 3 H) 4.33 - 4.57 (m, 1 H) 7.31 (d, *J*=8.1 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.60 - 7.66 (m, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 8.15 (s, 1 H) 8.50 (d, *J*=8.3 Hz, 1 H) 12.24 (br. s., 1 H).

Example 11-33: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 - 2.60 (m, 2 H) 2.66 (s, 3 H) 2.93 (d, *J*=6.8 Hz, 2 H) 4.43 - 4.63 (m, 1 H) 7.33 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.42 (m, 1 H) 7.46 (t,

J=7.8 Hz, 1 H) 7.58 - 7.66 (m, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 8.74 (d, *J*=8.3 Hz, 1 H) 8.98 (s, 2 H) 12.28 (br. s., 1 H).

Example 11-34: 1H NMR (400 MHz, MeOD) δ ppm 2.15 (s, 3 H) 2.67 (d, *J*=6.6 Hz, 2 H) 2.98 (dd, *J*=13.9, 8.3 Hz, 1 H) 3.03 (dd, *J*=14.1, 6.8 Hz, 1 H) 4.62 - 4.77 (m, 1 H) 5.57 (s, 1 H) 6.16 (s, 1 H) 7.27 - 7.32 (m, 1 H) 7.32 - 7.41 (m, 3 H) 7.46 - 7.54 (m, 3 H) 7.56 (t, *J*=1.8 Hz, 1 H) 7.65 (s, 1 H) 8.55 (d, *J*=8.6 Hz, 1 H).

Example 11-35: 1H NMR (400 MHz, CD_3OD) δ ppm 2.42 (s, 3 H) 2.63 (d, *J*=6.3 Hz, 2 H) 2.99 (d, *J*=7.1 Hz, 2 H) 4.59 - 4.73 (m, 1 H) 7.25 - 7.30 (m, 1 H) 7.30 - 7.37 (m, 3 H) 7.41 - 7.50 (m, 3 H) 7.53 (t, *J*=1.8 Hz, 1 H) 8.15 (s, 1 H).

Example 11-36: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 - 2.61 (m, 2 H) 2.87 (dd, *J*=13.1, 5.6 Hz, 1 H) 2.94 (dd, *J*=13.4, 7.6 Hz, 1 H) 4.41 - 4.60 (m, 1 H) 7.29 - 7.38 (m, 3 H) 7.45 (ddd, *J*=8.7, 4.2, 2.8 Hz, 1 H) 7.49 (d, *J*=6.8 Hz, 2 H) 7.56 (dd, *J*=6.8, 2.5 Hz, 1 H) 7.71 (s, 1 H) 8.53 (s, 1 H) 8.59 (d, *J*=8.6 Hz, 1 H) 12.26 (br. s., 1 H).

Example 11-37: 1H NMR (400 MHz, CD_3OD) δ ppm 1.32 (t, J=7.6 Hz, 3 H) 2.66 (d, J=6.8 Hz, 2 H) 2.83 (q, J=7.6 Hz, 2 H) 2.98 (dd, J=13.6, 7.8 Hz, 1 H) 3.03 (dd, J=14.7, 6.8 Hz, 1 H) 4.61 - 4.80 (m, 1 H) 7.13 (dd, J=18.9, 10.1 Hz, 1 H) 7.25 - 7.32 (m, 1 H) 7.32 - 7.37 (m, 2 H) 7.37 - 7.45 (m, 3 H) 7.54 (s, 1 H).

Example 11-38: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.15 (t, *J* = 7.73 Hz, 3 H) 2.39 (d, *J* = 6.8 Hz, 2 H) 2.79 (d, *J* = 6.8 Hz, 2 H) 3.46 – 3.56 (m, 2 H) 3.91 – 4.01 (m, 2 H) 4.21 – 4.29 (m, 1 H) 7.14 – 7.17 (m, 1 H) 7.28 (d, *J* = 8.3 Hz, 2 H) 7.39 – 7.42 (m, 1 H) 7.48 (t, *J* = 7.83 Hz, 1 H) 7.61 – 7.64 (m, 3 H) 7.69 – 7.70 (m, 1 H) 7.84 (d, *J* = 8.4 Hz, 1 H) 12.23 (br s, 1 H).

Example 11-39: 1H NMR (400 MHz, Methanol-d4) δ ppm 2.39 – 2.56 (m, 6 H) 2.87 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.6 Hz, 1 H) 2.94 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.1 Hz, 1 H) 4.43 – 4.50 (m, 1 H) 7.15 – 7.20 (m, 1 H) 7.31 – 7.35 (m, 3 H) 7.45 – 7.48 (m, 3 H).

Example 11-40: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.24-2.37 (m, 4H), 2.73 (dd, 1H, J = 7.83, 13.4 Hz), 2.88 (dd, 1H, J = 7.33, 13.4 Hz), 3.93 (s, 1H), 4.26-4.36 (m, 1H), 5.35 (bs,

1H), 7.33 (d, 2H, J = 8.08 Hz), 7.38-7.43 (m, 1H), 7.48 (t, 1H, J = 7.83 Hz), 7.63 (d, 3H, J = 8.34 Hz), 7.70 (t, 1H, J = 2.02 Hz), 7.73 (d, 1H, J = 9.09 Hz), 12.26 (bs, 2H).

Example 11-41: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.21-2.33 (m, 4H), 2.65-2.81 (m, 2H), 4.02 (d, 1H, J = 4.04 Hz), 4.24-4.32 (m, 1H), 5.56 (bs, 1H), 7.27 (d, 2H, J = 8.34 Hz), 7.37-7.42 (m, 1H), 7.47 (t, 1H, J = 7.83 Hz), 7.58 (d, 2H, J = 8.34 Hz), 7.60-7.64 (m, 1H), 7.69 (t, 1H, J = 1.77 Hz), 7.96 (d, 1H, J = 8.84 Hz), 12.03 (bs, 1H), 12.60 (bs, 1H).

Example 11-42: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.22-2.37 (m, 4H), 2.74 (dd, 1H, J = 8.34, 13.4 Hz), 2.86 (dd, 1H, J = 6.82, 13.4 Hz), 3.34 (s, 3H), 3.62 (d, 1H, J = 2.78 Hz), 4.34-4.44 (m, 1H), 7.31 (d, 2H, J = 8.34 Hz), 7.38-7.43 (m, 1H), 7.48 (t, 1H, J = 7.83 Hz), 7.63 (d, 3H, J = 8.34 Hz), 7.71 (s, 1H), 7.89 (d, 1H, J = 9.35 Hz).

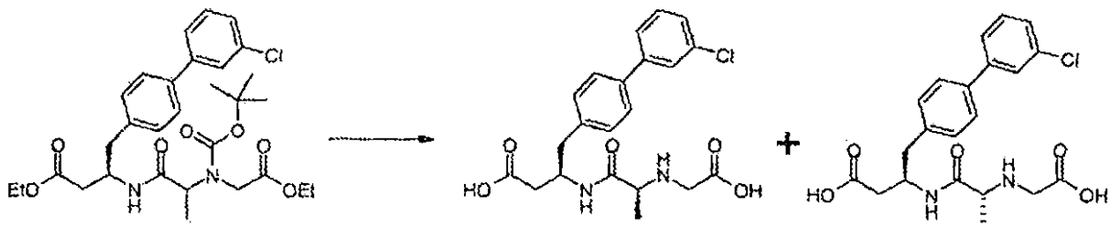
Example 11-43: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.17-2.37 (m, 4H), 2.64-2.81 (m, 2H), 3.37 (s, 3H), 3.77 (d, 1H, J = 4.04 Hz), 4.25-4.34 (m, 1H), 7.25 (d, 2H, J = 8.08 Hz), 7.38-7.42 (m, 1H), 7.47 (t, 1H, J = 7.83 Hz), 7.56-7.64 (m, 3H), 7.68 (t, 1H, J = 1.77 Hz), 8.05 (d, 1H, J = 8.84 Hz), 12.05 (bs, 1H), 12.89 (bs, 1H).

Example 11-44: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.20-2.39 (m, 4H), 2.65-2.87 (m, 2H), 4.37-4.56 (m, 1H), 4.91 (d, 0.5H, J = 2.78 Hz), 5.04 (d, 0.5H, J = 3.03 Hz), 7.29 (d, 2H, J = 8.34 Hz), 7.38-7.43 (m, 1H), 7.47 (t, 1H, J = 7.83 Hz), 7.58-7.65 (m, 3H), 7.69 (t, 1H, J = 1.77 Hz), 8.27 (d, 1H, J = 8.59 Hz), 12.05 (bs, 1H), 13.57 (bs, 1H).

Example 11-45: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.10 (d, *J*=7.1 Hz, 3 H), 2.17 - 2.37 (m, 4 H), 2.57 - 2.78 (m, 3 H), 4.19 - 4.31 (m, *J*=9.2, 9.2, 4.5, 4.3 Hz, 1 H), 7.30 (d, *J*=8.1 Hz, 2 H), 7.37 - 7.42 (m, 1 H), 7.47 (t, *J*=7.8 Hz, 1 H), 7.57 - 7.65 (m, 3 H), 7.70 (t, *J*=1.8 Hz, 1 H), 7.86 (d, *J*=8.8 Hz, 1 H), 12.21 (br. s., 2 H).

Example 11-46: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.45 (dd, *J*=6.6, 3.5 Hz, 1 H), 2.82 (d, *J*=7.1 Hz, 1 H), 3.88 (dd, *J*=20.2, 15.2 Hz, 1 H), 4.03 (s, 1 H), 4.29 - 4.41 (m, 1 H), 7.29 (d, *J*=8.3 Hz, 1 H), 7.37 - 7.43 (m, 1 H), 7.48 (t, *J*=8.0 Hz, 1 H), 7.62 (d, *J*=8.3 Hz, 2 H), 7.70 (t, *J*=1.8 Hz, 1 H), 7.89 (d, *J*=8.8 Hz, 1 H), 11.65 - 13.45 (m, 1 H).

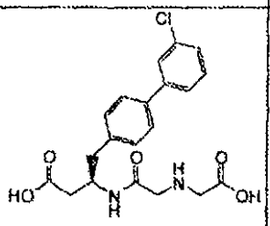
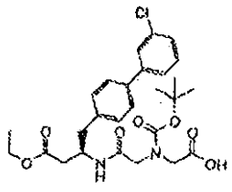
Example 11-47 /48: (R)-3-[(S)-2-(Carboxymethyl-amino)-propionylamino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid and (R)-3-[(R)-2-(Carboxymethyl-amino)-propionylamino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid



To a solution of (R)-3-[2-(tert-butoxycarbonyl-ethoxycarbonylmethyl-amino)-propionylamino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid ethyl ester (290 mg, 0.504 mmol) in THF (3 ml) and MeOH (0.5 ml) at room temperature is added 2M NaOH (1.009 ml, 2.017 mmol). The reaction is stirred at room temperature over night. The mixture is concentrated to dryness and the crude i taken up in DCM (3.00 ml), to which is added TFA (3.89 ml, 50.4 mmol) and the mixture is stirred at room temperature for 2hr. The reaction is concentrated for HPLC purification. Reverse phase HPLC [25 to 50% ACN-H_2O (0.1%TFA) over 10 min by Sunfire C18 column] give (R)-3-[(S)-2-(Carboxymethyl-amino)-propionylamino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid and (R)-3-[(R)-2-(Carboxymethyl-amino)-propionylamino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid.

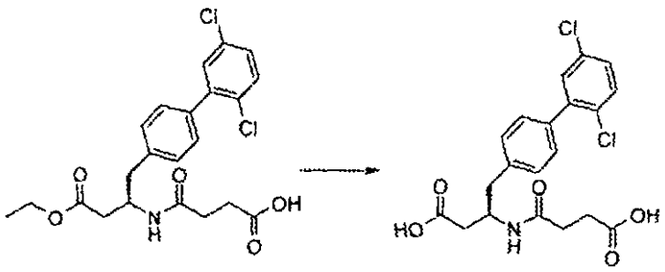
(R)-3-[(S)-2-(Carboxymethyl-amino)-propionylamino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (d, J=7.1 Hz, 3 H), 2.40 (dd, J=15.7, 8.3 Hz, 1 H), 2.51 - 2.56 (m, 1 H), 2.76 (dd, J=13.4, 8.1 Hz, 1 H), 2.87 (dd, J=13.4, 5.3 Hz, 1 H), 3.43 - 3.52 (m, 3 H), 3.67 (q, J=6.7 Hz, 1 H), 4.25 - 4.36 (m, 1 H), 7.30 (d, J=8.3 Hz, 2 H), 7.38 - 7.43 (m, 1 H), 7.48 (t, J=7.8 Hz, 1 H), 7.59 - 7.65 (m, 3 H), 7.70 (t, J=1.8 Hz, 1 H), 8.41 (d, J=8.3 Hz, 1 H). HRMS: Calcd for $C_{21}H_{23}ClN_2O_5$: 418.1295; found: m/z 418.1307. LCMS (condition A): 419 (M+1); retention time = 0.93 min; (R)-3-[(R)-2-(Carboxymethyl-amino)-propionylamino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (d, J=6.8 Hz, 3 H), 2.41 - 2.49 (m, 0 H), 2.51 - 2.57 (m, 1 H), 2.73 (dd, J=13.4, 9.1 Hz, 1 H), 2.91 (dd, J=13.4, 4.8 Hz, 1 H), 3.55 - 3.67 (m, 2 H), 3.67 - 3.74 (m, 1 H), 4.26 - 4.40 (m, 1 H), 7.29 (d, J=8.3 Hz, 2 H), 7.39 - 7.44 (m, 0 H), 7.48 (t, J=7.8 Hz, 0 H), 7.59 - 7.65 (m, 3 H), 7.69 (t, J=1.8 Hz, 1 H), 8.43 (d, J=8.6 Hz, 1 H). HRMS: Calcd for $C_{21}H_{23}ClN_2O_5$: 418.1295; found: m/z 418.1305. LCMS (condition A): 419 (M+1); retention time = 0.99 min.

Following compounds are prepared using similar procedure as described in example 11-47/48:

Example #	Product	Starting material	HPLC-RT (condition)	MS (M+1)
Example 11-49	 (R)-3-[2-(Carboxymethyl-amino)-acetylamino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid		1.12 min. (A)	405.2

Example 11-49: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.39 – 2.50 (m, 2 H) 2.77 – 2.89 (m, 2 H) 3.61 – 3.71 (m, 2 H) 3.81 (s, 2 H) 4.26 – 4.35 (m, 1 H) 7.31 (d, *J* = 8.3 HZ, 2 H) 7.40 – 7.43 (m, 1 H) 7.47 – 7.50 (m, 1 H) 7.62 – 7.65 (m, 3 H) 7.69 – 7.70 (m, 1 H) 8.49 (d, *J* = 7.3 Hz, 1 H).

Example 12-1: Synthesis of (*R*)-4-(1-carboxy-3-(3'-chlorobiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid

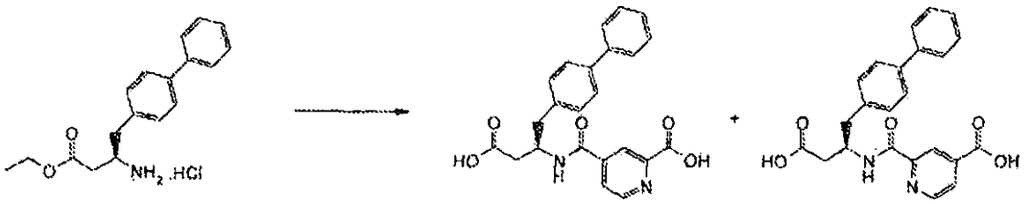


To a solution of (*R*)-4-(1-(2',5'-dichlorobiphenyl-4-yl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid (106 mg, 0.234 mmol) in THF (2 ml) and MeOH (0.1 ml), 1M aqueous NaOH solution (1.406 mL, 1.406 mmol) is added at room temperature. After stirring for 4.5

hours, the reaction is quenched with 0.1 M aqueous HCl (3 ml), and the products are extracted with EtOAc. The combined organic layer is washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude is triturated in DCM. The precipitates are collected on a funnel, washed with DCM, and dried under reduced pressure to give (*R*)-4-(1-carboxy-3-(3'-chlorobiphenyl-4-yl)propan-2-ylamino)-4-oxobutanoic acid (64.0 mg) as white solid; HPLC retention time = 1.24 minutes (condition A); MS (m+1) = 424.07; 1H NMR (400 MHz, CD_3OD) δ ppm 2.38-2.42 (m, 2 H) 2.45 - 2.57 (m, 4 H) 2.87 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.6 Hz, 1 H) 2.95 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.1 Hz, 1 H) 4.44 - 4.51 (m, 1 H) 7.30 - 7.37 (m, 6 H) 7.47 (d, *J* = 8.4 Hz, 1 H).

Example 13-1: Synthesis of (R)-4-(1-(biphenyl-4-yl)-3-carboxypropan-2-ylcarbamoyl)picolinic acid

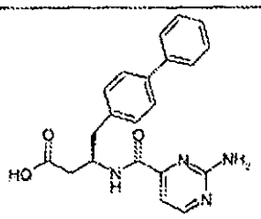
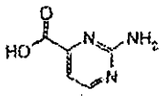
Example 13-2: Synthesis of (R)-2-(1-(biphenyl-4-yl)-3-carboxypropan-2-ylcarbamoyl)isonicotinic acid



To a solution of (R)-ethyl 3-amino-4-(biphenyl-4-yl)butanoate hydrochloride (200 mg, 0.625 mmol), 2,4-pyridinedicarboxylic acid hydrate (151 mg, 0.813 mmol), EDCI (132 mg, 0.688 mmol) and 1-hydroxy-7-azabenzotriazole (94 mg, 0.688 mmol) in DMF (6 ml), DIPEA (0.164 ml, 0.938 mmol) is added. The reaction mixture is allowed to stir for 3 hours. Then, the reaction mixture is diluted with H_2O. The precipitated solid is collected on a funnel and dried under reduced pressure. To a solution of the crude in THF (8 ml) and MeOH (1 ml), 1 M aqueous NaOH (2.5 ml, 2.5 mmol) is added. After stirring for 1 hour, the reaction is quenched with 5% citric acid and brine, and the products are extracted with EtOAc. The organic layer is washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue is purified by preparative HPLC using a gradient of 20% MeCN/water (0.1 % TFA) to 100% MeCN to give (R)-4-(1-(biphenyl-4-yl)-3-carboxypropan-2-ylcarbamoyl)picolinic acid and (R)-2-(1-(biphenyl-4-yl)-3-carboxypropan-2-

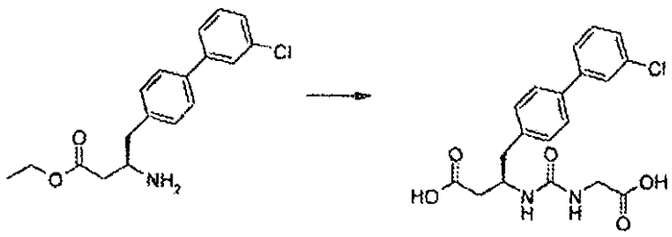
ylcarbamoyl)isonicotinic acid as white solids, respectively (Example 13-1: 33 mg; Example 13-2: 36 mg). Example 13-1, HPLC retention time = 1.50 minutes (condition D); MS (m+1) = 405.1; 1H NMR (400 MHz, DMSO-d6) δ ppm 2.53 - 2.62 (m, 2 H) 2.88 - 2.97 (m, 2 H) 4.50 - 4.59 (m, 1 H) 7.31 - 7.35 (m, 3 H) 7.42 - 7.45 (m, 2 H) 7.57 - 7.64 (m, 4 H) 7.89 (dd, J = 5, 1.6 Hz, 1 H) 8.83 (dd, J = 5, 0.8 Hz, 1 H) 8.37 (dd, J = 1.6, 0.8 Hz) 8.89 (d, J = 8.3 Hz, 1 H). Example 13-2, HPLC retention time = 1.24 minutes (condition A); MS (m+1) = 405.1; 1H NMR (400 MHz, DMSO-d6) δ ppm 2.52 - 2.68 (m, 2 H) 2.91 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 6.1 Hz, 1 H) 3.01 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 8.1 Hz, 1 H) 4.56 - 4.65 (m, 1 H) 7.29 - 7.34 (m, 3 H) 7.41 - 7.45 (m, 2 H) 7.55 - 7.64 (m, 4 H) 7.99 (dd, J = 5, 1.6 Hz, 1 H) 8.34 (dd, J = 1.6, 0.8 Hz, 1 H) 8.84 (dd, J = 5, 0.8 Hz, 1 H) 8.90 (d, J = 9.1 Hz, 1 H) 12.26 (br s, 1 H) 13.87 (br s, 1 H).

Following compounds are prepared using similar procedure as described in example 13-1 and 13-2:

Example #	Product	Condition	HPLC-RT (condition)	MS (M+1)
Example 13-3	 (R)-3-(2-aminopyrimidine-4-carboxamido)-4-(biphenyl-4-yl)butanoic acid	 PyBOP, DIPEA, DMF, RT ; aq. NaOH, THF, MeOH, RT	1.37 min. (A)	377.0

Example 13-3: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.55 (d, J = 6.6 Hz, 2 H) 2.91 (A of ABX, J_{ab} = 13.6 Hz, J_{ax} = 6.3 Hz, 1 H) 2.96 (B of ABX, J_{ab} = 13.6 Hz, J_{bx} = 7.6 Hz, 1 H) 4.46 - 4.55 (m, 1 H) 6.86 (br s, 2 H) 7.02 (d, J = 4.8 Hz, 1 H) 7.28 - 7.36 (m, 3 H) 7.42 - 7.46 (m, 2 H) 7.58 - 7.65 (m, 4 H) 8.39 (d, J = 9.1 Hz, 1 H) 8.45 (d, J = 4.8 Hz, 1 H).

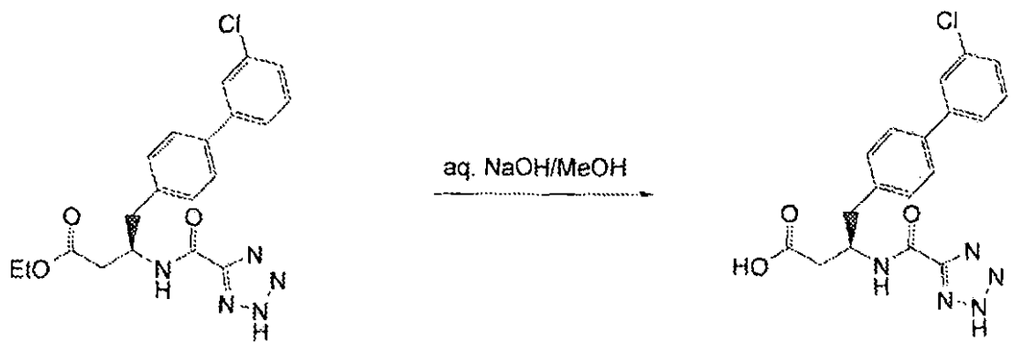
Example 14-1: Synthesis of (R)-3-(3-Carboxymethyl-ureido)-4-(3'-chloro-biphenyl-4-yl)-butyric acid



To a solution of intermediate 16-1 (90 mg, 0.254 mmol) and ethyl isocyanatoacetate (39.4 mg, 0.305 mmol) in DMF (3 mL) is added pyridine (2.93 g, 37.1 mmol) and the mixture is stirred at room temperature for 2 hours. The solvent is removed under reduced pressure and the residue is used directly in the next step.

Next, the above residue is dissolved in EtOH (1 mL) and 1N NaOH (3 mL, 3 mmol) is added. The mixture is stirred at room temperature for 2 hours then is acidified with 1N HCl. The mixture is extracted with EtOAc and the organic phase is washed with water, brine then dried over sodium sulfate. The solvent is removed under reduced pressure and the residue purified by preparative HPLC using a gradient of 10% MeCN/water to 100% MeCN (+0.1% TFA). Lyophilization of the proper fractions gives the title compound; HPLC Retention time 0.98 minutes (condition C); MS 391.3 (M+1); 1H NMR (400 MHz, DMSO-d6): δ ppm 2.34 (d, J=7.33 Hz, 2H), 2.79 (d, J=6.57 Hz, 2H), 3.67 (d, J=5.56 Hz, 2H), 4.04-4.12 (m, 1H), 6.15 (t, J=5.81 Hz, 1H), 6.23 (d, J=8.34 Hz, 1H), 7.28-7.30 (m, 2H), 7.39-7.42 (m, 1H), 7.48 (t, J = 7.83 Hz, 1H), 7.62-7.65 (m, 3H), 7.71 (t, J=1.77 Hz, 1H), 12.32 (s, br, 2H).

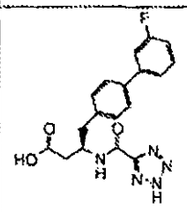
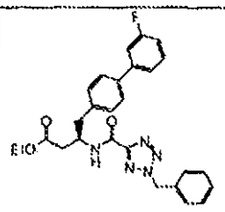
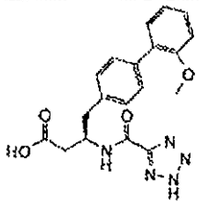
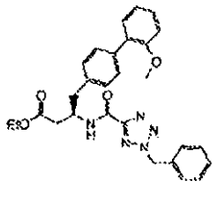
Example 15-1: (R)-4-(3'-Chloro-biphenyl-4-yl)-3-[(2H-tetrazole-5-carbonyl)-amino]-butyric acid



To a suspension of the starting material in MeOH (5 ml) at room temperature is added NaOH (2mL, 6.00 mmol) and the mixture is stirred until the reaction was completed. The reaction mixture is acidified to pH <4 and purified by HPLC (15% to 60% acetonitrile-H_2O with 0.1%TFA) to give (R)-4-(3'-chloro-biphenyl-4-yl)-3-[(2H-tetrazole-5-carbonyl)-amino]-butyric acid (80 mg).

HPLC retention time = 0.95 minutes (condition B); MS (m+1) = 386.1; 1H NMR (400 MHz, DMSO-d_6) d ppm 2.52 - 2.61 (m, 1 H), 2.61 - 2.72 (m, 1 H), 2.84 - 2.99 (m, 2 H), 4.51 - 4.64 (m, 1 H), 7.31 (d, J=8.1 Hz, 2 H), 7.36 - 7.41 (m, 1 H), 7.46 (t, J=7.8 Hz, 1 H), 7.61 (d, J=8.3 Hz, 3 H), 7.68 (t, J=1.9 Hz, 1 H), 9.31 (d, J=8.8 Hz, 1 H), 12.32 (br. s., 1 H).

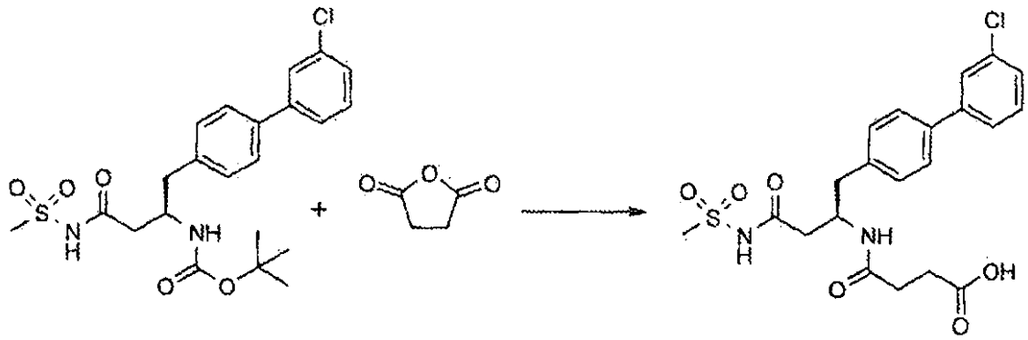
Following compounds are prepared using similar procedure as described in example 15-1:

Example #	Product	Starting material and hydrolysis condition	HPLC-RT (condition)	MS (M+1)
Example 15-2	 (R)-4-(3'-Fluoro-biphenyl-4-yl)-3-[(2H-tetrazole-5-carbonyl)-amino]-butyric acid	 1 atm. H2, Pd/C, EtOH, RT Followed by aq. NaOH and EtOH	1.26 min. (A)	370.2
Example 15-3	 (R)-4-(2'-Methoxy-biphenyl-4-yl)-3-[(2H-tetrazole-5-carbonyl)-amino]-butyric acid	 1 atm. H2, Pd/C, EtOH, RT Followed by aq. NaOH and EtOH	1.24 min. (A)	382.2

Example 15-2: 1H NMR (400 MHz, DMSO-d_6) d ppm 2.52 - 2.72 (m, 2 H), 2.86 - 3.00 (m, 2 H), 4.52 - 4.65 (m, 1 H), 7.11 - 7.20 (m, 1 H), 7.31 (d, J=8.1 Hz, 2 H), 7.43 - 7.51 (m, 3 H), 7.61 (d, J=8.3 Hz, 2 H), 9.28 (d, J=8.8 Hz, 1 H), 12.29 (br. s., 1 H).

Example 15-3: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 - 2.60 (m, J=15.9, 5.8 Hz, 1 H), 2.67 (dd, J=15.9, 7.8 Hz, 1 H), 2.87 (dd, J=13.6, 5.8 Hz, 1 H), 2.95 (dd, J=13.6, 8.3 Hz, 1 H), 3.73 (s, 3 H), 4.52 - 4.64 (m, 1 H), 7.00 (td, J=7.4, 1.1 Hz, 1 H), 7.08 (d, J=9.1 Hz, 1 H), 7.22 - 7.27 (m, 3 H), 7.28 - 7.34 (m, 1 H), 7.37 (d, J=8.3 Hz, 2 H), 9.30 (d, J=8.8 Hz, 1 H), 12.28 (br. s., 1 H).

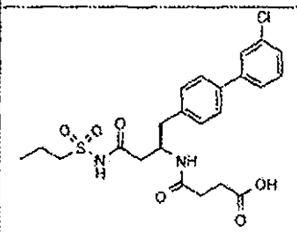
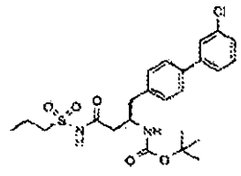
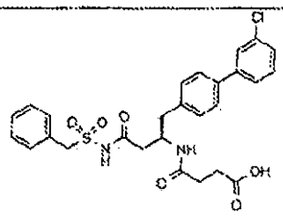
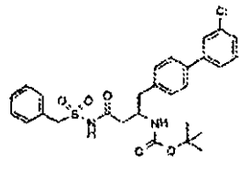
Example 16-1: N-[(R)-1-(3'-chloro-biphenyl-4-ylmethyl)-3-methanesulfonylamino-3-oxo-propyl]-succinamic acid

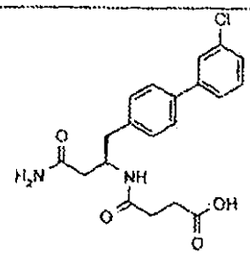
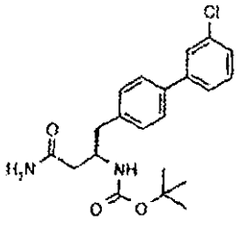


[(R)-1-(3'-Chloro-biphenyl-4-ylmethyl)-3-methanesulfonylamino-3-oxo-propyl]-carbamic acid tert-butyl ester (150 mg, 0.321 mmol) is treated with 4M HCl in dioxane. After being stirred at room temperature for 1h, the reaction mixture is concentrated *in vacuo*. To this residue in DCM (2 mL) are added succinic anhydride (48.2 mg, 0.482 mmol) and triethylamine (0.112 mL, 0.803 mmol). After being stirred at room temperature for 2h, the reaction mixture is diluted with EtOAc and washed with 1M HCl and brine. The organic layer is dried over Na_2SO_4 and cocentrated. The residue is purified by reverse phase HPLC (SunFire C18, 0.1%TFA in H_2O/CH_3CN) to give N-[(R)-1-(3'-chloro-biphenyl-4-ylmethyl)-3-methanesulfonylamino-3-oxo-propyl]-succinamic acid (63 mg). HPLC retentions time = 1.32 minutes (condition A); MS (m+1) = 467; 1H NMR (400 Mz, DMSO-d6) δ ppm 2.22-2.29 (m, 2 H), 2.32-2.54 (m, 4 H), 2.77 (d, 2 H, J = 6.82 Hz), 3.17 (s, 3 H), 4.31 (dt, 1 H, J = 7.33, 13.9 Hz), 7.28 (d, 2 H, J = 8.08 Hz), 7.38-7.43 (m, 1 H), 7.48 (t, 1 H, J = 7.83 Hz), 7.62 (d, 3 H, J

= 8.34 Hz), 7.70 (t, 1 H, J = 2.02 Hz), 7.89 (d, 1 H, J = 8.34 Hz), 11.70 (s, 1 H), 12.04 (s, 1 H).

Following compounds are prepared using similar procedure as described in example 16-1:

Example #	Product	Starting material	HPLC-RT (condition)	MS (M+1)
Example 16-2	 N-[(R)-1-(3'-Chloro-biphenyl-4-ylmethyl)-3-oxo-3-(propane-1-sulfonylamino)-propyl]-succinamic acid		1.26 min. (condition A)	495
Example 16-3	 N-[(R)-1-(3'-Chloro-biphenyl-4-ylmethyl)-3-oxo-3-phenylmethanesulfonyl amino-propyl]-succinamic acid		1.34 min. (condition A)	543

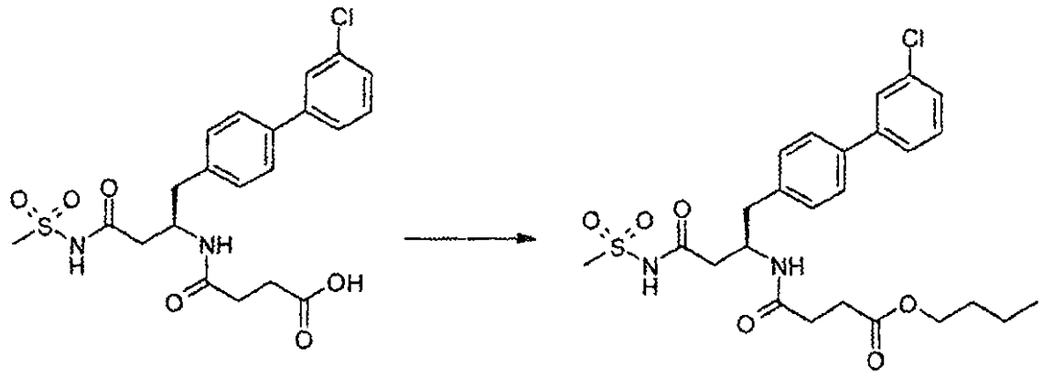
Example 16-4	 N-[(R)-2-Carbamoyl-1-(3'-chloro-biphenyl-4-ylmethyl)-ethyl]-succinamic acid		1.33 min. (condition A)	389

Example 16-2: 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.96 (t, 3 H, *J* = 7.33 Hz), 1.66 (dd, 2 H, *J* = 7.33, 15.2 Hz), 2.25 (t, 2 H, *J* = 7.07 Hz), 2.31-2.45 (m, 4 H), 2.76 (d, 2 H, *J* = 6.82 Hz), 3.25-3.32 (m, 2 H), 4.30 (dd, 1 H, *J* = 7.83, 14.7 Hz), 7.28 (d, 2 H, *J* = 8.34 Hz), 7.38-7.43 (m, 1 H), 7.48 (t, 1 H, *J* = 7.83 Hz), 7.63 (d, 3 H, *J* = 8.08 Hz), 7.70 (t, 1 H, *J* = 1.77 Hz), 7.89 (d, 1 H, *J* = 8.34 Hz), 11.61 (s, 1 H), 12.04 (s, 1 H).

Example 16-3: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.24-2.31 (m, 2 H), 2.34-2.40 (m, 2 H), 2.44 (d, 2 H, *J*= 6.82 Hz), 2.78 (d, 2 H, *J* = 6.82 Hz), 4.26-4.36 (m, 1 H), 4.67 (s, 2 H), 7.25-7.33 (m, 4 H), 7.34-7.43 (m, 4 H), 7.48 (t, 1 H, *J* = 7.58 Hz), 7.63 (d, 3 H, *J* = 8.34 Hz), 7.70 (t, 1 H, *J* = 1.77 Hz), 7.92 (d, 1 H, *J* = 8.34 Hz), 11.60 (s, 1 H), 12.05 (s, 1 H).

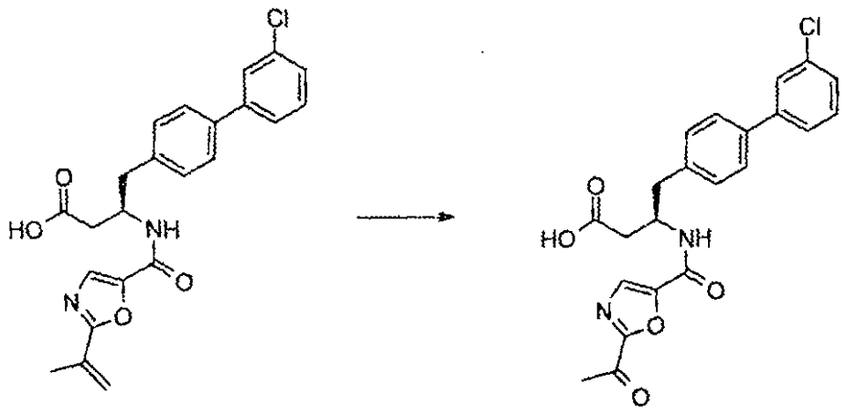
Example 16-4: 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.19-2.29 (m, 4H), 2.36 (dd, 2H, *J* = 6.57, 6.57 Hz), 2.72 (dd, 1H, *J*= 7.83, 13.6 Hz), 2.81 (dd, 1H, *J* = 5.31, 13.6 Hz), 4.17-4.27 (m, 1H), 6.83 (s, 1H), 7.28 (d, 3H, *J* = 8.34 Hz), 7.38-7.43 (m, 1H), 7.47 (t, 1H, *J* = 7.83 Hz), 7.58-7.65 (m, 3H), 7.69 (t, 1H, *J* = 1.77 Hz), 7.78 (d, 1H, *J* = 8.34 Hz), 12.05 (s, 1H).

Example 16-5: Synthesis of N-[(R)-1-(3'-chloro-biphenyl-4-ylmethyl)-3-methanesulfonylamino-3-oxo-propyl]-succinamic acid butyl ester



To a solution of N-[(R)-1-(3'-chloro-biphenyl-4-ylmethyl)-3-methanesulfonylamino-3-oxo-propyl]-succinamic acid (50 mg, 0.107 mmol) in *n*-butanol (2 mL) is added thionyl chloride (9.38 µL, 0.128 mmol). The reaction mixture is warmed to 50 °C and stirred for 1 h. After cooling to room temperature, the reaction mixture is concentrated and purified by reverse phase HPLC (SunFire C18, 0.1%TFA in H_2O/CH_3CN) to give N-[(R)-1-(3'-chloro-biphenyl-4-ylmethyl)-3-methanesulfonylamino-3-oxo-propyl]-succinamic acid butyl ester (32 mg). HPLC retentions time = 1.56 minutes (condition A); MS (m+1) = 523; 1H NMR (400 Mz, DMSO-d6) δ ppm 0.86 (t, 3H, *J* = 7.33 Hz), 1.22-1.34 (m, 2H), 1.45-1.55 (m, 2H), 2.23-2.33 (m, 2H), 2.35-2.44 (m, 3H), 2.45-2.55 (m, 3H), 2.71-2.83 (m, 1H), 3.18 (s, 3H), 3.96 (t, 2H, *J* = 6.57 Hz), 4.27-4.38 (m, 1H), 7.28 (d, 2H, *J* = 8.08 Hz), 7.37-7.43 (m, 1H), 7.48 (t, 1H *J* = 7.83 Hz), 7.62 (d, 3H, *J* = 8.34 Hz), 7.70 (s, 1H), 7.91 (d, 1H, *J* = 8.34 Hz), 11.71 (s, 1H).

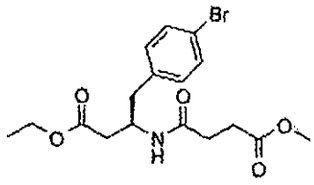
Example 17: (R)-3-(2-acetyloxazole-5-carboxamido)-4-(3'-chlorobiphenyl-4-yl)butanoic acid



To a solution of (R)-4-(3'-chlorobiphenyl-4-yl)-3-(2-(prop-1-en-2-yl)oxazole-5-carboxamido)butanoic acid (60 mg, 0.14 mmol) in DCM (2 mL) and MeOH (2 mL) at -78°C is bubbled ozone for 30 seconds. After 30 seconds ozone is removed and oxygen is bubbled for 10 minutes. After bubbling oxygen for 10 minutes the -78°C bath is removed and the reaction is quenched with polymer supported triphenylphosphine and the reaction is stirred at room temperature for 2 hours. After 2 hours the reaction is filtered to remove triphenylphosphineoxide on supported polymer and the filtrate is collected and concentrated under reduced pressure. The obtained residue is purified by RP-HPLC (SunFire C18, H_2O(0.1% TFA)/CH_3CN), and then lyophilized to give (R)-3-(2-acetyloxazole-5-carboxamido)-4-(3'-chlorobiphenyl-4-yl)butanoic acid (13 mg). HPLC retention time = 1.67 minutes (condition D); MS (m+1) = 427.0; 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.53 - 2.59 (m, 2 H) 2.60 (s, 3 H) 2.87 (dd, *J*=10.9, 3.3 Hz, 1 H) 2.94 (dd, *J*=10.9, 5.1 Hz, 1 H) 4.46 - 4.60 (m, 1 H) 7.31 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.43 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.62 (d, *J*=8.3 Hz, 3 H) 7.69 (t, *J*=1.9 Hz, 1 H) 7.94 (s, 1 H) 8.86 (d, *J*=8.6 Hz, 1 H) 12.31 (br. s., 1 H).

Starting materials or intermediates are prepared in following manner:

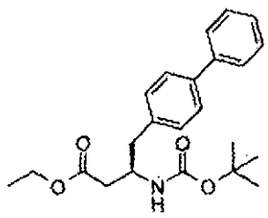
Intermediate 1: (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate



To (*R*)-ethyl-4-(4-bromophenyl-4-yl)-3-(*tert*-butoxycarbonylamino)butanoate (2.02 g, 5.23 mmol) is added a solution of 4M HCl in 1,4-dioxane (13.1 mL, 52.3 mmol) at room temperature. After stirring for 1 hour, the reaction mixture is concentrated under reduced pressure to give (*R*)-3-amino-4-bromophenyl-4-yl-butyric acid ethyl ester hydrochloride. To a solution of (*R*)-3-amino-4-bromophenyl-4-yl-butyric acid ethyl ester hydrochloride is added succinic anhydride (0.707 g, 7.06 mmol) and DIPEA (2.06 mL, 11.8 mmol) in dichloromethane (20 mL) and allowed to stir for 4 hours. The reaction is quenched with 0.1 M aqueous HCl. The products are extracted with ethyl acetate and washed with brine. The organic layer is dried over $Na2_SO_4$, filtered, and concentrated under reduced pressure to give (R)-4-(1-(4-bromophenyl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid (2.26 g). To a solution of the obtained residue (2.26 g) in toluene (25 mL) and MeOH (25 mL),

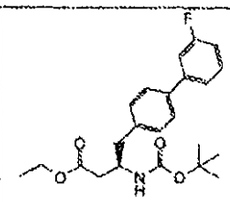
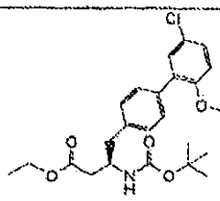
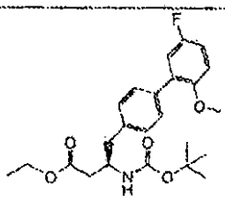
$TMSCHN_2$ in hexanes (5.85 ml, 11.70 mmol) is added portionwise at room temperature under nitrogen. The reaction mixture is allowed to stir for 1.5 hour, then quenched with AcOH (0.5 mL; 8.78 mmol), and the solution is stirred for 10 minutes. The solution is concentrated, and the obtained residue is purified by flash column chromatography on 40 g silica gel (eluent: heptane/EtOAc = 100:0 to 0:100) to give (R)-ethyl 4-(4-bromophenyl)-3-(4-methoxy-4-oxobutanamido)butanoate (1.92 g). HPLC retention time = 1.04 minutes (condition B); MS (ES+) = 400 (m+1), 402.0 (m+3; 100%); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, *J*=7.2 Hz, 3 H) 2.40 - 2.53 (m, 4 H) 2.60 - 2.64 (m, 2 H) 2.79 (A of ABX, Jab = 13.7 Hz, Jax = 7.85 Hz, 1 H) 2.90 (B of ABX, Jab = 13.7 Hz, Jbx = 6.65 Hz, 1 H) 3.68 (s, 3 H) 4.10 – 4.22 (m, 2 H) 4.39 – 4.47 (m, 1 H) 6.29 (br d, J = 8.6 Hz, 1 H) 7.06 (d, J = 8.4 Hz, 2 H) 7.40 – 7.42 (m, 2 H).

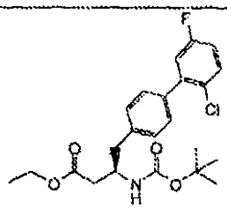
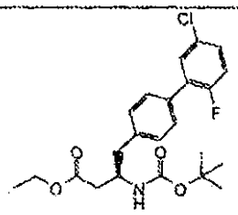
Intermediate 2: (*R*)-ethyl 4-(biphenyl-4-yl)-3-(tert-butoxycarbonylamino)butanoate



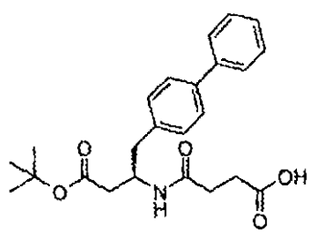
A mixture of (*R*)-ethyl 4-(4-bromophenyl)-3-(tert-butoxycarbonylamino)butanoate (1.5 g, 3.88 mmol), phenylboronic acid (0.710 g, 5.82 mmol), Pd(Ph3P)4 (0.449 g, 0.388 mmol) and aqueous Na_2CO_3 (3.88 mL, 7.77 mmol) in toluene (25 mL) is allowed to stir at 95 °C under nitrogen for 14 hours. The reaction mixture is cooled to room temperature and quenched with brine. The mixture is extracted twice with ethylacetate, and the combined organic layer is washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue is purified by silica gel flash column chromatography (heptane/EtOAc = 100:0 to 50:50) to give (*R*)-ethyl 4-(biphenyl-4-yl)-3-(tert-butoxycarbonylamino)butanoate (1.30 g); HPLC retention time = 1.61 minutes (condition B); MS (ES+) = 328.0 (m-tBu+2); 284.1 (m-Boc+2; 100%); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, J = 7.1 Hz, 3 H) 2.48 (A of ABX, Jab = 16.1 Hz, Jax = 5.9 Hz, 1 H) 2.53 (B of ABX, Jab = 16.0 Hz, Jbx = 5.3 Hz, 1 H) 2.83 – 3.00 (m, 2 H) 4.14 – 4.19 (m, 3 H) 5.06 (br s) 7.26 – 7.27 (m, 2 H) 7.31-7.35 (m, 2 H) 7.43 (t, J = 7.6 Hz, 2H) 7.52 -7.58 (m, 4 H).

Following intermediates are prepared using similar procedure as described for intermediate 2:

Intermediate #	Product	Condition	HPLC-RT (condition)	MS (ES+; 100%)
Intermediate 2-2	 (R)-ethyl 3-(tert-butoxycarbonylamino)-4-(3'-fluorobiphenyl-4-yl)butanoate	Pd(PPh3)4, 3-fluorobenzeneboronic acid, aq. 2M Na2CO3, toluene, 95 °C	1.61 min. (B)	302.1 (m-BOC+2)
Intermediate 2-3	 (R)-ethyl 3-(tert-butoxycarbonylamino)-4-(5'-chloro-2'-methoxybiphenyl-4-yl)butanoate	$PdCl_2(dppf).CH_2Cl_2$ complex, 5-chloro-2-methoxyphenylboronic acid, aq. 2M Na2CO3, toluene, 95 °C	1.58 min. (B)	348.1 (m-BOC+2)
Intermediate 2-4	 (R)-ethyl 3-(tert-butoxycarbonylamino)-4-(5'-fluoro-2'-methoxybiphenyl-4-yl)butanoate	$PdCl_2(dppf).CH_2Cl_2$ complex, 5-fluoro-2-methoxyphenylboronic acid, aq. 2M Na_2CO_3, toluene, 95 °C	1.42 min. (B)	332.2 (m-BOC+2)

Intermediate 2-5	 (R)-ethyl 3-(tert-butoxycarbonylamino)-4-(2'-chloro-5'-fluorobiphenyl-4-yl)butanoate	$Pd(PPh_3)_4$, 2-chloro-5-fluorophenylboronic acid, aq. 2M Na_2CO_3, toluene, 95 °C	1.49 min. (B)	336.1 (m-BOC+2)
Intermediate 2-6	 (R)-ethyl 3-(tert-butoxycarbonylamino)-4-(5'-chloro-2'-fluorobiphenyl-4-yl)butanoate	$Pd(PPh_3)_4$, 5-chloro-2-fluorophenylboronic acid, aq. 2M Na2CO3, DME, 95 °C	1.47 min. (B)	336.1 (m-BOC+2)

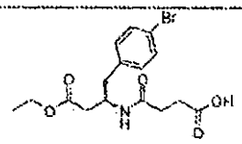
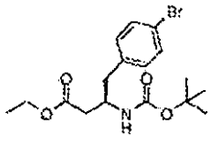
Intermediate 3: (*R*)-4-(1-(biphenyl-4-yl)-4-tert-butoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid



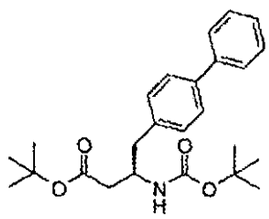
To (*R*)-tert-butyl 4-(biphenyl-4-yl)-3-(tert-butoxycarbonylamino)butanoate (26.4 mg, 0.064 mmol) is added 4M HCl in 1,4-dioxane (0.321 ml, 1.283 mmol) at room temperature. The reaction mixture is stirred for 45 minutes and concentrated under reduced pressure. To a solution of the obtained residue in dichloromethane (0.4 mL) is added succinic anhydride (7.70 mg, 0.077 mmol) and DIPEA (0.013 mL, 0.077 mmol). The reaction mixture is allowed to stir at room temperature for 14 hours and concentrated under reduced pressure. The

obtained residue is purified by RP-HPLC (SunFire C-18, H_2O(0.1%TFA)/CH_3CN) to give (R)-4-(1-(biphenyl-4-yl)-4-tert-butoxy-4-oxobutan-2-ylamino)-4-oxobutanoic acid (9.5 mg). HPLC retention time = 1.70 minutes (condition A); MS (ES+) = 412.1 (m+1); 356.0 (m-tBu+2; 100%); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.48 (s, 9 H) 2.36 -2.51 (m, 4 H) 2.64 – 2.67 (m, 2 H) 2.87 (A of ABX, Jab = 13.5 Hz, Jax = 5.7 Hz, 1 H), 2.97 (Jab = 13.5 Hz, Jbx = 6.2 Hz, 1 H) 7.24-7.26 (m, 2 H) 7.31-7.35 (m, 1 H) 7.43 (t, J = 7.75 Hz, 2 H) 7.53(d, J = 8.0 Hz, 2 H) 7.57 (d, J = 7.6 HZ, 2 H).

Following intermediates are prepared using similar procedure as described in intermediate 3:

Intermediate #	Product	Starting Material	HPLC-RT (condition)	MS (M+1)
Intermediate 3-2	 (R)-4-(4-Bromo-phenyl)-3-(3-carboxy -propionylamino)-butyric acid ethyl ester		0.90 min. (B)	385.9

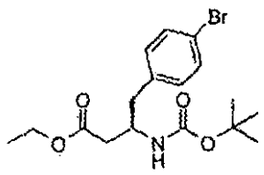
Intermediate 4: (R)-tert-butyl 4-(biphenyl-4-yl)-3-(tert-butoxycarbonylamino)butanoate



A solution of (R)-2-(biphenyl-4-ylmethyl)-4-tert-butoxy-4-oxobutanoic acid (100 mg, 0.294 mmol), DPPA (0.076 mL, 0.353 mmol) and Et_3N (0.049 mL, 0.353 mmol) in Toluene (1.5 mL) is allowed to stir at 100 °C under nitrogen for 2 hours. tBuOH (0.281 ml, 2.94 mmol) is added and the mixture is refluxed for 5 hours at the same temperature. The reaction is cooled to room temperature, and the solvent is removed. Ethyl acetate is added to the obtained residue, and the organic layer is washed with 5% aqueous citric acid, H_2O,

saturated aqueous $NaHCO_3$, and brine. The organic layer is dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue is purified by flash column chromatography on 40 g of silica gel (heptane/EtOAc = 100:0 to 50:50) to give the corresponding isocyanate (35.7 mg). The obtained isocyanate is dissolved in tBuOH (0.3 mL) and the solution is allowed to stir at 80 °C for 20 hours. The reaction mixture is concentrated, and the residue is purified by flash column chromatography on 12 g of silica gel (heptane/EtOAc = 100:0 to 70:30) to give (R)-tert-butyl 4-(biphenyl-4-yl)-3-(tert-butoxycarbonylamino)butanoate (26.4 mg, 22%). HPLC retention time = 1.74 minutes (*condition B*); MS (ES+) = 356.0 (*m-tBu+2*) 300.0 (*m-tBux2+3*; 100%); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.41 (s, 9 H) 1.47 (s, 9 H) 2.36 (A of ABX, Jab = 15.6 Hz, Jax = 6.2 Hz, 1 H) 2.44 (B of ABX, Jab = 15.5 Hz, Jbx = 5.45 Hz) 2.82 – 2.97 (m, 2 H) 4.15 (br s) 5.09 (br d) 7.6-7.35 (m, 3H) 7.41 – 7.45 (m, 2 H) 7.51-7.56 (m, 4 H).

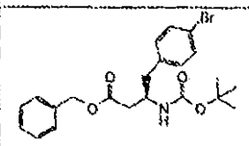
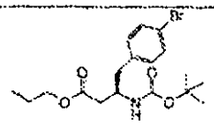
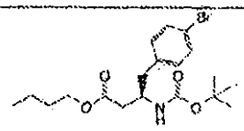
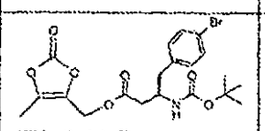
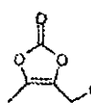
Intermediate 5: (R)-ethyl 4-(4-bromophenyl)-3-(tert-butoxycarbonylamino)butanoate

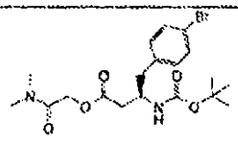
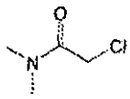
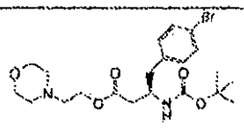
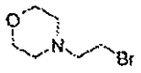


To a suspension of (R)-4-(4-bromophenyl)-3-(tert-butoxycarbonylamino)butanoic acid (9.98 g, 27.9 mmol) and $NaHCO_3$ (4.68 g, 55.7 mmol) in DMF (45 mL) is added Ethyl iodide (6.75 mL, 84 mmol) at room temperature under nitrogen. After stirring for 71 hours, the reaction is quenched with H_2O (300 mL), and then precipitated solid is collected and washed with H_2O (500 mL) to give (R)-ethyl 4-(4-bromophenyl)-3-(tert-butoxycarbonylamino)butanoate (10.25 g, 94%). HPLC retention time = 1.48 minutes (condition B); MS (ES+) = 329.9 (m-tBu+2); 286.0 (m-Boc+2; 100%); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.27 (t, J = 7.2 Hz, 3 H) 1.40 (s, 9 H), 2.43 (A of ABX, Jab = 15.8 Hz, Jax = 5.7 Hz, 1 H) 2.50 (B of ABX, Jab = 15.8 Hz, Jbx = 5.4 Hz, 1 H) 2.74 – 2.90 (m, 2 H) 4.11 (br s) 4.15 (q, J = 7.1 Hz, 2 H) 5.04 (br d) 7.07 (d, J = 8.3 Hz, 2 H) 7.40-7.43 (m, 2 H).

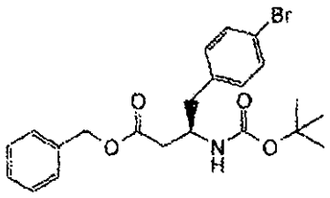
Following intermediates are prepared using similar procedure as described for intermediate 5:

Intermediate	Product	Condition	HPLC-RT	MS

#			(condition)	(ES+; 100%)
Intermediate 5-2	 (R)-benzyl 4-(4-bromophenyl)-3-(tert-butoxycarbonylamino)butanoate	BnBr, $NaHCO_3$, DMF, RT	1.56 min. (B)	348 (m-BOC+2)
Intermediate 5-3	 (R)-4-(4-Bromo-phenyl)-3-tert-butoxycarbonylamino-butyric acid propyl ester	n-propyl iodide, $NaHCO_3$, DMF, RT	1.47 min. (B)	400 (m+1)
Intermediate 5-4	 (R)-4-(4-Bromo-phenyl)-3-tert-butoxycarbonylamino-butyric acid butyl ester	n-butyl iodide, $NaHCO_3$, DMF, RT	1.55 min. (B)	414 (m+1)
Intermediate 5-5	 (R)-4-(4-Bromo-phenyl)-3-tert-butoxycarbonylamino-butyric acid 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester	 K_2CO_3, DMF, RT	1.28 min. (B)	470 (m+1)

Intermediate 5-6	 (R)-4-(4-Bromo-phenyl)-3-tert-butoxycarbonylamino-butyric acid dimethylcarbamoyl methyl ester	 K_2CO_3, DMF, RT	1.65 min. (B)	444 (m+1)
Intermediate 5-7	 (R)-4-(4-Bromo-phenyl)-3-tert-butoxycarbonylamino-butyric acid 2-morpholin-4-yl-ethyl ester	 K_2CO_3, DMF, RT	1.19 min. (B)	471 (m+1)

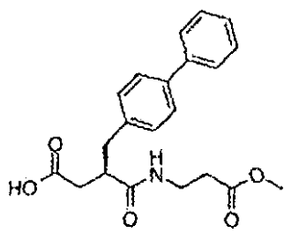
Intermediate 5-2: (R)-benzyl 4-(4-bromophenyl)-3-(tert-butoxycarbonylamino)butanoate



To a suspension of (R)-4-(4-bromophenyl)-3-(tert-butoxycarbonylamino)butanoic acid (5.02 g, 14.01 mmol) and $NaHCO_3$ (3.53 g, 42.0 mmol) in DMF (20 mL) is added Benzyl bromide (5.10 mL, 42 mmol) at room temperature under nitrogen. After stirring for 46 hours, the reaction is diluted with H_2O (200 mL), and then precipitated solid is collected and washed with H_2O (500 mL) and then with heptane (200 ml) to give (R)-benzyl 4-(4-bromophenyl)-3-(tert-butoxycarbonylamino)butanoate (5.61 g, 89%). HPLC retention time = 1.56 minutes (condition B); MS (ES+) = 392.1 (m-tBu+2); 348.1 (m-Boc+2; 100%); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.39 (s, 9 H) 2.48 (A of ABX, Jab = 15.9 Hz, Jax = 5.6 Hz, 1 H) 2.54 (B of ABX, Jab = 15.9 Hz, Jbx = 5.3 Hz, 1 H) 2.72 – 2.88 (m, 2 H) 4.11 (br s, 1 H) 5.02

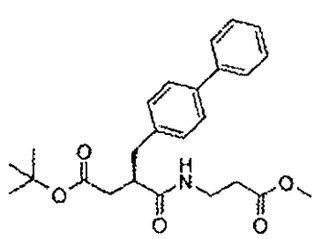
(br s, 1 H) 5.10 (A of AB, J = 12.1 Hz, 1 H) 5.16 (A of AB, J = 12.1 Hz, 1 H) 7.00 (d, J = 8.1 Hz, 2 H) 7.34-7.39 (m, 7 H).

Intermediate 6: (R)-3-(biphenyl-4-ylmethyl)-4-(3-methoxy-3-oxopropylamino)-4-oxobutanoic acid



To a solution of (R)-tert-butyl 3-(biphenyl-4-ylmethyl)-4-(3-methoxy-3-oxopropylamino)-4-oxobutanoate (40 mg, 0.094 mmol) in DCM (0.5 mL), TFA (0.15 mL) is added at room temperature. The mixture is allowed to stir for 2 hours, and then concentrated under reduced pressure to give (R)-3-(biphenyl-4-ylmethyl)-4-(3-methoxy-3-oxopropylamino)-4-oxobutanoic acid (33.5 mg, 96%). HPLC retention time = 1.20 minutes (condition A); MS (m+1) = 370.1; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.21 – 2.29 (m, 1 H) 2.38 – 2.45 (m, 1 H) 2.62 – 2.66 (m, 1 H) 2.75 – 3.00 (m ,4 H) 3.29 – 3.37 (m, 1 H) 3.45 – 3.53 (m, 4 H) 6.12 (br s, 1 H) 7.23 (d, J = 8 Hz, 2 H) 7.32 – 7.35 (m, 1 H) 7.41 -7.45 (m, 2 H) 7.53 (d, J = 8.1 Hz, 2 H) 7.56 – 7.59 (m, 2 H).

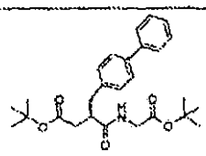
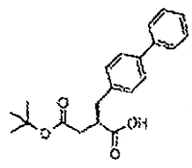
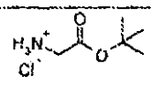
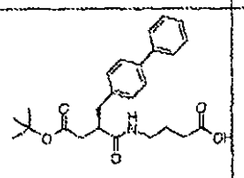
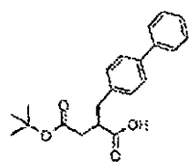
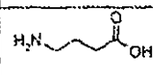
Intermediate 7: (R)-tert-butyl 3-(biphenyl-4-ylmethyl)-4-(3-methoxy-3-oxopropylamino)-4-oxobutanoate



A solution of (R)-2-(biphenyl-4-ylmethyl)-4-tert-butoxy-4-oxobutanoic acid (142 mg, 0.417 mmol), 3-amino-propionic acid methyl ester hydrochloride (76 mg, 0.542 mmol), WSC

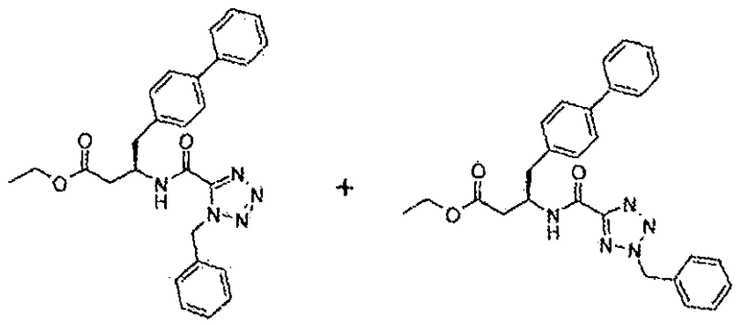
hydrochloride (120 mg, 0.626 mmol), 1-hydroxy-7-azabenzotriazole (85 mg, 0.626 mmol) and DIPEA (0.219 ml, 1.251 mmol) in DMF (4 mL) is allowed to stir at room temperature under nitrogen for 13 hours. The reaction is quenched with H_2O. The products are extracted with ethyl acetate, washed with aqueous 1M HCl and then with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue is purified by flash column chromatography on 12 g of silica gel (heptane/EtOAc = 70:30 to 0:100) to give (R)-tert-butyl 3-(biphenyl-4-ylmethyl)-4-(3-methoxy-3-oxopropylamino)-4-oxobutanoate (164 mg, 91%). HPLC retention time = 1.59 minutes (condition A); MS (ES+) = 425.4 (m); 369.4 (m-tBu+1; 100%); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.24 – 2.44 (m, 2 H) 2.67 - 2.79 (m, 3 H) 2.89 -2.96 (m, 1 H) 3.28 – 3.36 (m, 1 H) 3.45 – 3.53 (m, 1 H) 7.23 (d, J = 5.8 Hz, 2 H) 7.33 (t, J = 7.35 Hz, 1 H) 7.41 – 7.44 (m, 2 H) 7.51 (d, J = 8.1 Hz, 2 H) 7.58 (d, J = 7.4 Hz, 2 H).

Following intermediates are prepared using similar procedure as described in intermediate 7:

Intermediate #	Product	Starting Material	Condition	HPLC-RT (condition)	MS (M+1)
Intermediate 7-2	 (R)-3-Biphenyl-4-ylmethyl-N-tert-butoxycarbonylmethyl-succinamic acid tert-butyl ester		 WSC.HCl, HOAt, DIPEA, DMF, rt	1.64 min. (B)	454.1
Intermediate 7-3	 (R)-3-Biphenyl-4-ylmethyl-N-(3-carb oxy-propyl)-succinamic acid		 WSC.HCl, HOAt, DIPEA, DMF, rt	1.71 min. (A)	426.1

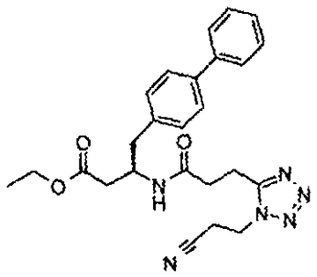
	tert-butyl ester				

Intermediate 8: (R)-3-[(1-benzyl-1H-tetrazole-5-carbonyl)-amino]-4-biphenyl-4-yl-butyric acid ethyl ester and (R)-3-[(2-benzyl-2H-tetrazole-5-carbonyl)-amino]-4-biphenyl-4-yl-butyric acid ethyl ester



(*R*)-ethyl 4-(biphenyl-4-yl)-3-(tert-butoxycarbonylamino)butanoate (117 mg, 0.305 mmol) is treated with 4M HCl dioxane solution (2 mL). After stirring for 0.5 hour, the reaction mixture is concentrated under reduced pressure. To a solution of the obtained residue and Et_3N (0.106 mL, 0.763 mmol) in DCM (3 mL) is added benzyl-*H*-tetrazole-5-carbonyl chloride (mixture of 1 and 2-benzyl isomers, 82 mg, 0.366 mmol, prepared according to *J.Med.Chem.* **1986**, 29, 538-549). After stirring for 10 minutes, Et_3N (0.106 mL, 0.763 mmol) and the acid chloride (82 mg, 0.366 mmol) are added. After stirring for 0.5 hour, the reaction mixture is diluted with ethyl acetate, washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography to give (R)-3-[(1-benzyl-1H-tetrazole-5-carbonyl)-amino]-4-biphenyl-4-yl-butyric acid ethyl ester and (R)-3-[(2-benzyl-2H-tetrazole-5-carbonyl)-amino]-4-biphenyl-4-yl-butyric acid ethyl ester. HPLC retention time = 1.51 minutes (condition D); MS = 470.0 (m+1); 1H NMR (400 MHz, CDCl3) δ ppm 1.27 (t, J=7.07, 7.07Hz, 3H), 2.57-2.70 (m, 2H), 3.00 (dd, J=7.58, 13.77Hz, 1H), 3.12 (dd, J=6.57, 13.77Hz, 1H), 4.12-4.23 (m, 2H), 4.71-4.80 (m, 1H), 5.80 (s, 2H), 7.27-7.45 (m, 9H), 7.52 (d, J=8.34Hz, 2H), 7.56 (d, J=8.46Hz, 2H), 7.75 (d, J=7.33Hz, 1H).

Intermediate 9: (R)-4-biphenyl-4-yl-3-{3-[1-(2-cyano-ethyl)-1H-tetrazol-5-yl]-propionylamino}-butyric acid ethyl ester



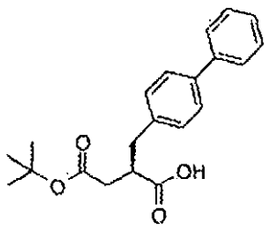
To a solution of (R)-4-biphenyl-4-yl-3-tert-butoxycarbonylamino-butyric acid ethyl ester (400 mg, 1.04 mmol) in DCM (10 mL) at room temperature is added TFA (2.009 mL, 26.1 mmol) and the mixture is stirred at room temperature for 1 hour. The mixture is concentrated under reduced pressure. To the obtained TFA salt in DCM (10 mL) at ice bath temperature is added succinic anhydride (125 mg, 1.25 mmol) and followed by TEA (0.363 mL, 2.61 mmol). The reaction is stirred at room temperature for 16 hours. The mixture is concentrated under reduced pressure. The obtained residue is purified by flash chromatography (silica gel, 2% to 5% EtOH/DCM) give (R)-4-biphenyl-4-yl-3-(3-carboxy-propionylamino)-butyric acid ethyl ester (200 mg). HPLC retention time = 1.53 minutes (condition C); MS = 384 (m+1).

Next, to a solution of (R)-4-biphenyl-4-yl-3-(3-carboxy-propionylamino)-butyric acid ethyl ester (200 mg, 0.522 mmol) in THF (10 mL) at room temperature is added EDC HCl (120 mg, 0.626 mmol) and HOBT (96 mg, 0.626 mmol). The reaction is stirred at room temperature for 10 minutes then added 3-aminopropionitrile (0.046 ml, 0.626 mmol) and TEA (0.087 ml, 0.626 mmol). After 1 hour, 0.5 equivalent of EDC HCl, HOBT, and 3-aminopropionitrile are added and stirred for 16 hours. The reaction mixture is quenched by brine and is extracted with ethylacetate. The combined organic layer is washed with brine and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The obtained residue is purified by flash chromatography (silica gel, 2% to 5% EtOH/DCM) to give (R)-4-biphenyl-4-yl-3-[3-(2-cyano-ethylcarbamoyl)-propionylamino]-butyric acid ethyl ester (218 mg, 96% yield). HPLC retention time = 0.77 minutes (condition E); MS = 436 (m+1).

Next, to a solution of (R)-4-biphenyl-4-yl-3-[3-(2-cyano-ethylcarbamoyl)-propionylamino]-butyric acid ethyl ester (204 mg, 0.468 mmol) in THF (10 mL) at room temperature is added

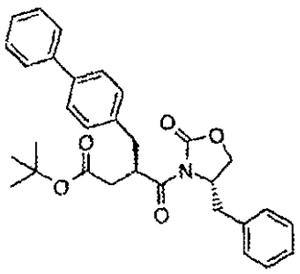
Ph_3P (307 mg, 1.17 mmol) and the mixture is stirred at room temperature for 10 minutes. Then to the mixture at ice bath temperature is added DIAD (0.228 ml, 1.171 mmol) and trimethylsilyl azide (0.155 ml, 1.171 mmol). The resulting mixture is slowly warmed up to room temperature and stirred for 16 hours. The reaction mixture is concentrated under reduced pressure. The obtained residue is purified by flash chromatography (silica gel, 1% to 3% EtOH/DCM) to give (R)-4-biphenyl-4-yl-3-{3-[1-(2-cyano-ethyl)-1H-tetrazol-5-yl]-propionylamino}-butyric acid ethyl ester (137 mg, 64% yield). HPLC retention time = 1.61 minutes (condition C); MS = 461 (m+1).

Intermediate 10: (R)-2-(biphenyl-4-ylmethyl)-4-tert-butoxy-4-oxobutanoic acid



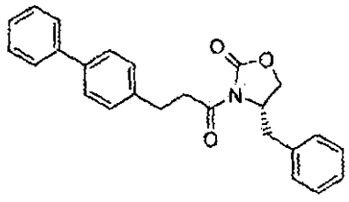
To a stirred solution of (R)-tert-butyl 4-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(biphenyl-4-ylmethyl)-4-oxobutanoate (1.20 g, 2.402 mmol) in a mixed solvent of THF (20 mL) and water (5 mL), a solution of aqueous H_2O_2 (0.960 mL, 9.61 mmol) and aqueous LiOH (4.80 ml, 4.80 mmol) is added at 0 °C during 5 minutes. After stirring for 1.5 hour, the reaction is quenched with saturated aqueous Na_2SO_3 (10 mL) at 0 °C, and allowed to stir for 10 minutes at the same temperature. The reaction mixture is warmed up to ambient temperature while stirring for 0.5 hour. Then, saturated aqueous $NaHCO_3$ and brine are added to the mixture. The product is extracted with ethyl acetate, washed with aqueous 1M HCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained residue is purified by flash column chromatography on 120 g of silica gel (heptane/EtOAc = 75:25 to 0:100) to give (R)-2-(biphenyl-4-ylmethyl)-4-tert-butoxy-4-oxobutanoic acid (765 mg, 93%). HPLC retention time = 1.63 minutes (condition D); MS = 338.6 (m-1); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.43 (s, 9 H) 2.41 (A of ABX, J_{ab}=16.67 Hz, J_{ax} = 4.55 Hz, 1 H) 2.52 - 2.67 (B of ABX, Jab = 16.75 Hz, Jbx = 8.45 Hz, 1 H) 2.74 - 2.89 (m, 1 H) 3.06 - 3.22 (m, 2 H) 7.22 - 7.29 (m, 2 H) 7.30 - 7.37 (m, 1 H) 7.43 (t, *J*=7.58 Hz, 2 H) 7.53 (d, *J*= 8.1 Hz, 2 H) 7.57 (d, J = 7.8 Hz, 2 H).

Intermediate 11: Synthesis of (R)-tert-butyl 4-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(biphenyl-4-ylmethyl)-4-oxobutanoate



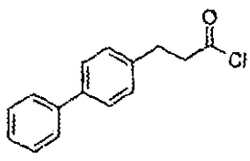
A stirred solution of (S)-4-benzyl-3-(3-(biphenyl-4-yl)propanoyl)oxazolidin-2-one (intermediate 12: 5.01 g, 13.00 mmol) in THF (180 mL) is cooled to -73.8 °C, and 1M THF solution of sodium hexamethyldisilylamide (14.30 mL, 14.30 mmol) is added during 5 minutes. After 30 minutes, a solution of tert-butyl bromoacetate (2.495 mL, 16.90 mmol) in THF (20 mL) is added dropwise during 5 minutes. The solution is stirred at -74 °C for 1 hour, and the reaction is quenched with saturated aqueous NH_4Cl (100 mL), and warmed up to ambient temperature. The precipitated solid is filtered off and washed with ethyl acetate (50 mL). The organic phase is separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue is suspended in MeOH (70 mL) and then filtered to collect the solid (5.9 g) as a mixture of the desired product and the starting material. The mixture is purified by flash column chromatography on 120 g of silica gel (heptane/EtOAc = 90:10 to 50:50) to give (R)-tert-butyl 4-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(biphenyl-4-ylmethyl)-4-oxobutanoate (2.40 g, 37%). HPLC retention time = 1.74 minutes (condition B); MS = 499.4 (m+); 443.4 (m-tBu+1; 100%); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.41 (s, 9 H) 2.42 (dd, *J*=16.67, 4.04 Hz, 1 H) 2.71 (ddd, *J*=16.55, 13.26, 9.60 Hz, 2 H) 2.87 (dd, *J*=16.93, 10.86 Hz, 1 H) 3.04 (dd, *J*=13.14, 6.32 Hz, 1 H) 3.32 (dd, *J*=13.39, 3.03 Hz, 1 H) 3.92 (t, *J*=8.34 Hz, 1 H) 4.07 (dd, *J*=8.97, 2.15 Hz, 1 H) 4.48 - 4.58 (m, 2 H) 7.20 - 7.30 (m, 3 H) 7.30 - 7.36 (m, 5 H) 7.42 (t, *J*=7.58 Hz, 2 H) 7.52 (d, J = 8.1 Hz, 2 H) 7.56 (d, J = 7.8 Hz, 2 H).

Intermediate 12: (S)-4-benzyl-3-(3-(biphenyl-4-yl)propanoyl)oxazolidin-2-one



To a 1.6 M solution of n-BuLi in hexane (12.1 mL, 19.3 mmol) is added dropwise a solution of (*S*)-(-)-4-benzyl-2-oxazolidinone (3.26 g, 18.4 mmol) in dry THF (80 mL) at -71.6 °C under nitrogen over 10 minutes. The solution is warmed up to -60.5 °C while the addition, and allowed to stir for 1 hour in dry ice/MeOH bath. 3-(Biphenyl-4-yl)propanoyl chloride (intermediate 13: 5.46 g, 22.31 mmol) in dry THF (20 mL) is added dropwise at -72 °C over 5 minutes. The solution is warmed up to -56.5 °C while the addition. After stirring 10 minutes at the same temperature, the reaction mixture is allowed to warm to room temperature and stirring is continued for 3 hours. The reaction mixture is filtered, and the collected precipitate is washed with 20 mL (10 mL x2) of MeOH and then with 150 mL of H_2O to give the desired product (4.26 g). The products in the mother liquor is extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained residue is suspended in 80 mL of MeOH, and the suspension is filtered and washed with 20 mL of MeOH (1.79 g). The two fractions are mixed to give (S)-4-benzyl-3-(3-(biphenyl-4-yl)propanoyl)oxazolidin-2-one (6.05 g, 85% in 2 steps). Retention time = 1.77 minutes (condition A); MS (m+1) = 387.3; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.77 (dd, *J*=13.39, 9.35 Hz, 1 H) 2.99 - 3.15 (m, 2 H) 3.20 - 3.43 (m, 3 H) 4.09 - 4.24 (m, 2 H), 4.68 (dddd, *J*=9.76, 6.73, 3.47, 3.28 Hz, 1 H) 7.18 (d, *J*=7.07 Hz, 2 H) 7.23 - 7.37 (m, 6 H) 7.42 (t, *J*=7.58 Hz, 2 H) 7.53 (d, J = 8.1 Hz, 2 H), 7.57 (d, J = 7.8 Hz, 2 H).

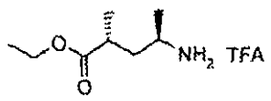
Intermediate 13: 3-(biphenyl-4-yl)propanoyl chloride



A mixture of 3-(4-biphenylyl)propionic acid (5 g, 22.10 mmol) and $SOCl_2$ (4.03 ml, 55.2 mmol) is refluxed under nitrogen at 85 °C for 1.5 hour. The reaction mixture is concentrated

under reduced pressure to give 3-(biphenyl-4-yl)propanoyl chloride (5.46 g). The material is used in the next step without further purification.

Intermediate 14: (2R,4R)-4-Amino-2-methyl-pentanoic acid ethyl ester trifluoroacetate

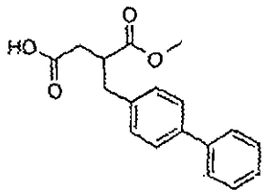


To a stirred solution of 2-(triphenylphosphanylidene)-propionic acid ethyl ester (3.11 g, 8.57 mmol) in methylene chloride (20 mL) is added a solution of 3,3-dimethyl-N-((R)-1-methyl-2-oxo-ethyl)-butyramide (J. Med. Chem. **41**, 6 (1998) (1.35 g, 7.79 mmol) in methylene chloride (20 mL) and the mixture is stirred at room temperature for 2 hours. The solvent is removed under reduced pressure and the residue is purified by column chromatography using a gradient of 10-50% heptane/EtOAc to give (E)-(R)-4-tert-butoxycarbonylamino-2-methyl-pent-2-enoic acid ethyl ester. ^{1}H-NMR (400 MHz, $CDCl_3$); δ ppm 1.22 (d, J=6.44 Hz, 3H), 1.30 (t, 3H), 1.43 (s, 9H), 1.91 (s, 3H), 4.19 (q, 2H), 6.51 (d, broad, J=7.45 Hz, 1H).

Next, a solution of (E)-(R)-4-tert-butoxycarbonylamino-2-methyl-pent-2-enoic acid ethyl ester (1.83 g, 7.11 mmol) in ethyl acetate (75 mL) is hydrogenated over 10% Pt/C (183 mg) at 1 atm for 18 hours. The catalyst is filtered through Celite and the solvent is removed under reduced pressure. The residue is purified by chiral HPLC to afford (2R,4R)-4-tert-butoxycarbonylamino-2-methyl-pentanoic acid ethyl ester, ^{1}H-NMR (400 MHz, $CDCl_3$); δ ppm 1.13 (t, 3H), 1.18 (m, 3H), 1.26 (t, 3H), 1.43 (s, 9H), 1.81 (s, 1H), 2.50 (m, 1H), 3.72 (m broad, 1H), 4.14 (m, 2H), 4.33 (m broad, 1H).

Next, (2R,4R)-4-tert-butoxycarbonylamino-2-methyl-pentanoic acid ethyl ester (142 mg, 0.548 mmol) is added to trifluoroacetic acid (5 mL). After 10 minutes, the solvent is removed under reduced pressure. Methylene chloride is added and the solvent is removed under reduced pressure to give (2R,4R)-4-amino-2-methyl-pentanoic acid ethyl ester trifluoroacetate. This material is used directly in the subsequent coupling reaction.

Intermediate 15: 2-Biphenyl-4-ylmethyl-succinic acid 1-methyl ester



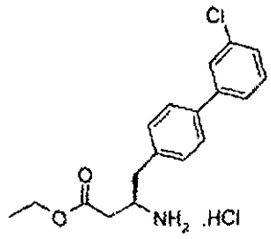
To a solution of (triphenylphosphanylidene)-acetic acid methyl ester (2.26 g, 6.77 mmol) in methylene chloride (25 mL) is added t-butyl bromoacetate (1.32 g, 6.77 mmol) and the mixture is stirred at room temperature for 48 hours. The solvent is removed under reduced pressure and the residue is purified by column chromatography using a gradient of 80-100% heptane/EtOAc to afford 2-(triphenylphosphanylidene)-succinic acid 4-tert-butyl ester 1-methyl ester. MS 449.3 (M+1).

Next, a mixture of 2-(triphenylphosphanylidene)-succinic acid 4-tert-butyl ester 1-methyl ester (700 mg, 1.561 mmol) and biphenyl-4-carboxaldehyde (278 mg, 1.419 mmol) in toluene (20 mL) is refluxed for 4 days. The solvent is removed under reduced pressure and the residue is purified by column chromatography using a gradient of 0-30% heptane/EtOAc to give 2-[1-biphenyl-4-yl-meth-(Z)-ylidene]-succinic acid 4-tert-butyl ester 1-methyl ester as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$); δ ppm 1.47 (s, 9H), 3.52 (s, 2H), 3.84 (s, 3H), 7.37 (t, 1H), 7.46 (t, 4H), 7.62 (t, 4H), 7.89 (s, 1H).

A solution of 2-[1-biphenyl-4-yl-meth-(Z)-ylidene]-succinic acid 4-tert-butyl ester 1-methyl ester (410 mg, 1.163 mmol) in ethyl acetate (20 mL) is hydrogenated over Pt/C (40 mg) at 1 atm for 18 hours. The catalyst is filtered through Celite and the solvent is removed under reduced pressure to give 2-biphenyl-4-ylmethyl-succinic acid 4-tert-butyl ester 1-methyl ester. The enantiomers are separated by chiral HPLC.

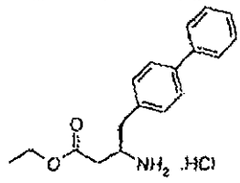
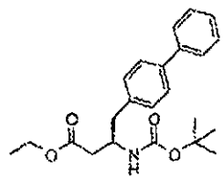
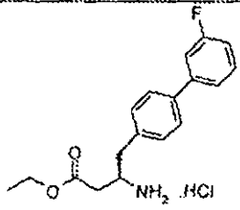
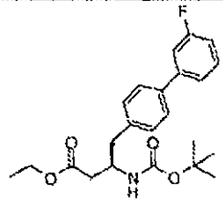
Next, 2-biphenyl-4-ylmethyl-succinic acid 4-tert-butyl ester 1-methyl ester (160 mg, 0.451 mmol) is added to trifluoroacetic acid (5 mL). After 10 minutes, the solvent is removed under reduced pressure. Methylene chloride is added and the solvent is removed under reduced pressure to give 2-biphenyl-4-ylmethyl-succinic acid 1-methyl ester. This material is used directly in the subsequent coupling reaction.

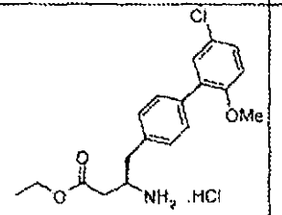
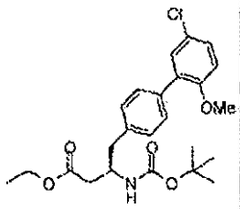
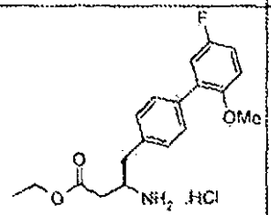
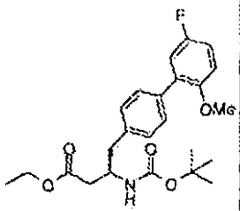
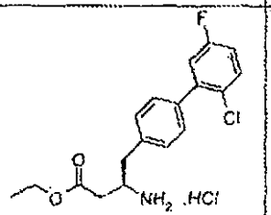
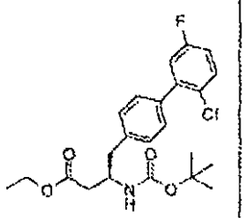
Intermediate 16-1: Synthesis of (*R*)-ethyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride

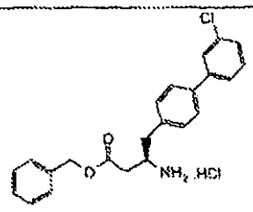
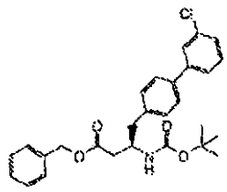
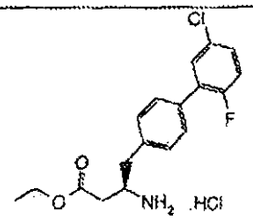
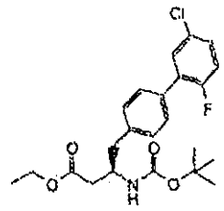


To (*R*)-ethyl 3-(tert-butoxycarbonylamino)-4-(3'-chlorobiphenyl-4-yl)butanoate (3.33 g, 7.97 mmol) is added a solution of 4 M HCl in 1,4-dioxane (19.9 mL, 18.0 mmol) at room temperature. After stirring for 0.5 hours, the reaction mixture is concentrated under reduced pressure to give (*R*)-ethyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride (2.90 g). HPLC retention time = 0.70 minutes (condition B); MS (m+1) = 318.26; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.19 – 1.24 (m, 3 H) 2.73 – 2.78 (m, 1 H) 2.84 – 2.91 (m, 1 H) 3.05 – 3.11 (m, 1 H) 3.50 – 3.54 (m, 1 H) 3.92 (br s, 1 H) 4.14 – 4.17 (m, 2 H) 7.29 – 7.53 (m, 8 H) 8.73 (br. s., 3 H).

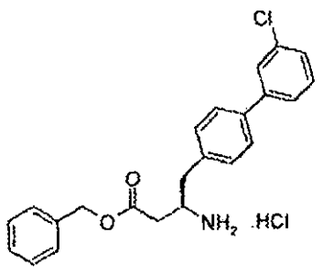
Following intermediates are prepared using similar procedure as described for intermediate 16-1:

Intermediate #	Product	Starting Material	Condition	HPLC-RT (condition)	MS (M+1)
Intermediate 16-2	 (R)-ethyl 3-amino-4-(biphenyl-4-yl)butanoate hydrochloride	 Intermediate 2	4M HCl/1,4-dioxane	0.89 min. (B)	284.1
Intermediate 16-3	 (*R*)-ethyl 3-amino-4-	 Intermediate 2-2	4M HCl/1,4-dioxane	0.94 min. (B)	302.1

	(3'-fluorobiphenyl-4-yl)butanoate hydrochloride				
Intermediate 16-4	 (*R*)-ethyl 3-amino-4-(5'-chloro-2'-methoxybiphenyl-4-yl)butanoate hydrochloride	 Intermediate 2-3	4M HCl/1,4-dioxane	0.94 min. (B)	348.2
Intermediate 16-5	 (*R*)-ethyl 3-amino-4-(5'-fluoro-2'-methoxybiphenyl-4-yl)butanoate hydrochloride	 Intermediate 2-4	4M HCl/1,4-dioxane	1.38 min. (A)	332.2
Intermediate 16-6	 (*R*)-ethyl 3-amino-4-(2'-chloro-5'-fluorobiphenyl-4-yl)butanoate hydrochloride	 Intermediate 2-5	4M HCl/1,4-dioxane	0.93 min. (B)	336.1

Intermediate 16-7	 (R)-benzyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate	 Intermediate 17-2	4M HCl/1,4-dioxane	1.20 min. (B)	380.2
Intermediate 16-8	 (*R*)-ethyl 3-amino-4-(5'-chloro-2'-fluorobiphenyl-4-yl)*butanoate*	 Intermediate 2-6	4M HCl/1,4-dioxane	0.88 min. (B)	336.1

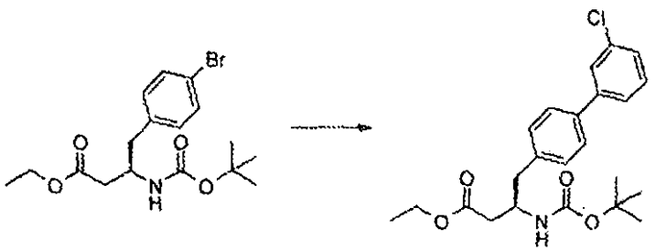
Intermediate 16-7: (R)-benzyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride



To (R)-benzyl 3-(tert-butoxycarbonylamino)-4-(3'-chlorobiphenyl-4-yl)butanoate (3.561 g, 7.42 mmol) is added a solution of 4 M HCl in 1,4-dioxane (18.55 mL, 74.2 mmol) at room temperature. After stirring for 4 hours, the reaction mixture is concentrated under reduced pressure to give (R)-benzyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride (3.11 g). HPLC retention time = 1.07 minutes (condition B); MS (m+1) = 380.1; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.81 (A of ABX, J_{ab} = 17.4 Hz, J_{ax} = 4.5 Hz, 1 H) 2.93 (B of ABX, J_{ab} = 17.4 Hz, J_{bx} = 7.6 Hz, 1 H) 3.03 – 3.09 (m, 1 H) 3.50 (dd, J = 4.9

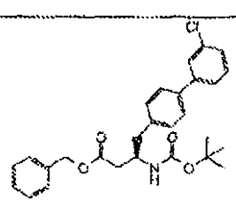
and 13.5 Hz, 1 H) 3.98 (br s, 1 H) 5.09 (s, 2 H) 7.24 – 7.22 (m, 9 H) 7.35 – 7.38 (m, 1 H) 7.42 (d, J = 8.1 Hz, 2 H) 7.48 – 7.49 (m, 1 H) 8.78 (br s, 3 H).

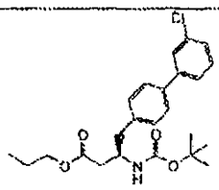
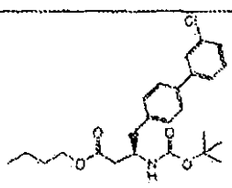
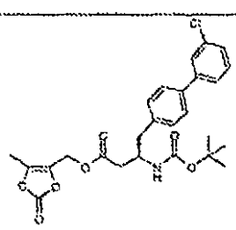
Intermediate 17-1: Synthesis of (*R*)-ethyl 3-(tert-butoxycarbonylamino)-4-(3'-chlorobiphenyl-4-yl)butanoate

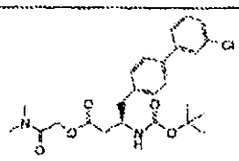
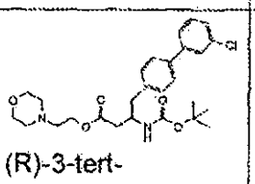


A mixture of (*R*)-ethyl 4-(4-bromophenyl)-3-(tert-butoxycarbonylamino)butanoate (4.89 g, 12.66 mmol), 3-chlorophenylboronic acid (2.97 g, 18.99 mmol), $Pd(PPh_3)_4$ (1.463 g, 1.266 mmol) and 2 M aqueous Na_2CO_3 (12.66 ml, 25.3 mmol) in 1,2-dimethoxyethane (100 ml) is allowed to stir at 95 °C under nitrogen for 3 hours. The reaction mixture is cooled to room temperature and quenched with brine. The two phases are separated. The mixture is extracted twice with ethyl acetate from the aqueous layer. The combined organic layer is washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained residue is purified by silica gel flash column chromatography (heptane/EtOAc = 100:0 to 70:30) to give (*R*)-ethyl 3-(tert-butoxycarbonylamino)-4-(3'-chlorobiphenyl-4-yl)butanoate (3.33 g); HPLC retention time = 1.44 minutes (condition B); MS (ES+) = 318.26 (m-BOC+2; 100%); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, *J* = 7.2 Hz, 3 H) 1.41 (s, 9 H) 2.47 (A of ABX, J_{ab} = 15.8 Hz, J_{ax} = 5.9 Hz, 1 H) 2.52 (B of ABX, J_{ab} = 15.8 Hz, J_{bx} = 5.4 Hz, 1 H) 2.83 – 2.89 (m, 1 H) 2.95 – 3.00 (m, 1 H) 4.17 (q, *J* = 7.2 Hz, 2 H) 4.18 (br s, 1 H) 5.07 (br s, 1 H) 7.26 – 7.37 (m, 4 H) 7.43 – 7.51 (m, 3 H) 7.55 (br t, *J* = 1.8 Hz, 1 H).

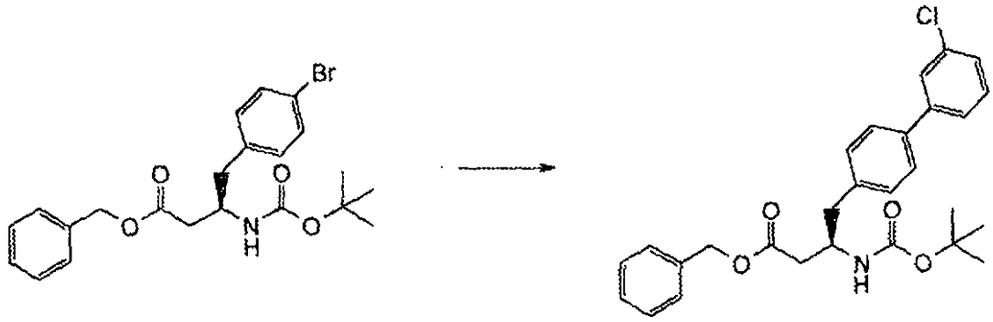
Following intermediates are prepared using similar procedure as described for intermediate 17-1:

Intermediate #	Product	Condition	HPLC-RT (condition)	MS (ES+; 100%)
Intermediate 17-2		$Pd(PPh_3)_4$, 3-chlorophenylboronic acid, aq. 2M	1.74 min. (B)	380.2 (m-BOC+2)

	(R)-benzyl 3-(tert-butoxycarbonylamino)-4-(3'-chlorobiphenyl-4-yl)butanoate	Na2CO3, toluene, 95 °C		
Intermediate 17-3	 (R)-3-tert-Butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-butyric acid propyl ester	$Pd(PPh_3)_4$, 3-chlorophenylboronic acid, aq. 2M Na2CO3, toluene, 95 °C	1.66 min. (B)	432 (m+1)
Intermediate 17-4	 (R)-3-tert-Butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-butyric acid butyl ester	$Pd(PPh_3)_4$, 3-chlorophenylboronic acid, aq. 2M Na2CO3, toluene, 95 °C	1.73 min. (B)	446 (m+1)
Intermediate 17-5	 (R)-3-tert-Butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-	$Pd(OAc)_2$, dicyclohexyl-(2',6'-dimethoxy-biphenyl-2-yl)-phosphane, 3-chlorophenylboronic acid, K_3PO_4, toluene, 95 °C	1.53 min. (B)	502 (m+1)

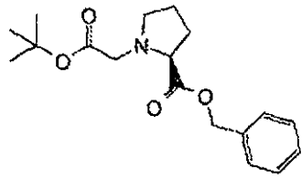
	butyric acid 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl ester			
Intermediate 17-6	 (R)-3-tert-Butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-butyric acid dimethylcarbamoyl methyl ester	$Pd(PPh_3)_4$, 3-chlorophenylboronic acid, K_3PO_4, DMF, 95 °C	1.51 min. (B)	475 (m+1)
Intermediate 17-7	 (R)-3-tert-Butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-butyric acid 2-morpholin-4-yl-ethyl ester	$Pd(PPh_3)_4$, 3-chlorophenylboronic acid, K_3PO_4, DMF, 95 °C	1.51 min. (B)	503 (m+1)

Intermediate 17-2: (R)-benzyl 3-(tert-butoxycarbonylamino)-4-(3'-chlorobiphenyl-4-yl)butanoate



A suspension of give (R)-benzyl 4-(4-bromophenyl)-3-(tert-butoxycarbonylamino)butanoate (2.00 g, 4.46 mmol), 3-chlorophenylboronic acid (1.046 g, 6.69 mmol), Pd(PPh3)4 (0.515 g, 0.446 mmol) and Na2CO3aq (4.46 ml, 8.92 mmol) in Toluene (30 ml) is allowed to stir under nitrogen at 95 °C for 19 hr. The reaction mixture is cooled to ambient temperature, and diluted with brine and EtOAc. The products are extracted twice with EtOAc, washed with brine, dried over MgSO4, filtered, and concentrated. The residue is purified by flash column chromatography on 90 g silica gel (eluent: heptane/EtOAc = 100:0 to 65:35) to give (R)-benzyl 3-(tert-butoxycarbonylamino)-4-(3'-chlorobiphenyl-4-yl)butanoate (1.03 g); HPLC retention time = 1.74 minutes (condition B); MS (ES+) = 380.2 (m-BOC+2; 100%); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.40 (s, 9 H) 2.52 (A of ABX, J_{ab} = 15.9 Hz, J_{ax} = 5.8 Hz, 1 H) 2.58 (B of ABX, J_{ab} = 15.9 Hz, J_{bx} = 5.6 Hz, 1 H) 2.81 – 2.98 (m, 2 H) 4.19 (br s, 1 H) 5.07 (br d, 1 H) 5.12 (A of AB, J = 12.3 Hz, 1 H) 5.17 (A of AB, J = 12.3 Hz, 1 H) 7.20 – 7.22 (m, 2 H) 7.28 – 7.39 (m, 7 H) 7.42 – 7.47 (m, 3 H) 7.53 – 7.54 (m, 1 H).

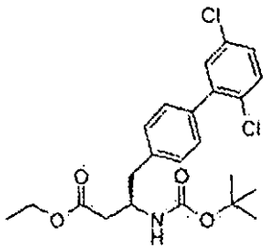
Intermediate 18: Synthesis of (S)-benzyl 1-(2-tert-butoxy-2-oxoethyl)pyrrolidine-2-carboxylate



To a suspension of (S)-benzyl pyrrolidine-2-carboxylate hydrochloride (700 mg, 2.90 mmol) and K_2CO_3 (1201 mg, 8.69 mmol) in DMF (7 ml), t-butyl bromoacetate (0.535 ml, 3.62 mmol) is added. After stirring for 71 hours, aqueous K2CO3 (1.5 g of K_2CO_3 / 40 ml of H_2O) is added to the reaction mixture. The products are extracted with EtOAc. The organic layer is washed twice with water and once with brine, dried over K_2CO_3, filtered, and concentrated to give (S)-benzyl 1-(2-tert-butoxy-2-oxoethyl)pyrrolidine-2-carboxylate (458 mg); HPLC

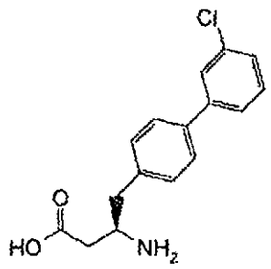
retention time = 1.38 minutes (condition D); MS (m+1) = 320.2; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.44 (s, 9 H) 1.81 – 2.03 (m, 3 H) 2.13 – 2.14 (m, 1 H) 2.82 – 2.88 (m, 1 H) 3.13 – 3.17 (m, 1 H) 3.46 (A of AB, *J* = 17.3 Hz, 1 H) 3.49 (B of AB, *J* = 17.3 Hz, 1 H) 3.73 (dd, *J* = 8.8 and 4.8 Hz, 1 H) 5.15 (A of AB, *J* = 12.4 Hz, 1 H) 5.17 (B of AB, *J* = 12.4 Hz, 1 H) 7.29 – 7.38 (m, 5 H).

Intermediate 19: Synthesis of (*R*)-ethyl 3-(tert-butoxycarbonylamino)-4-(2',5'-dichlorobiphenyl-4-yl)butanoate



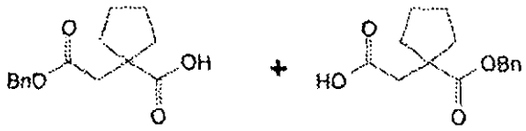
A mixture of (*R*)-ethyl 4-(4-bromophenyl)-3-(tert-butoxycarbonylamino)butanoate (1.005 g, 2.60 mmol), 2,5-dichlorophenylboronic acid (0.745 g, 3.90 mmol), Pd(PPh3)4 (0.301 g, 0.260 mmol) and 2 M aqueous Na_2CO_3 (2.60 ml, 5.20 mmol) in 1,2-dimethoxyethane (20 ml) is allowed to stir at 95 °C under nitrogen for 3 hours. The reaction mixture is cooled to room temperature and diluted with brine. The two phases are separated. The products are extracted twice with ethyl acetate (2 x 100 ml) from the aqueous layer. The combined organic layer is washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained residue is purified by silica gel flash column chromatography (heptane/EtOAc = 100:0 to 70:30) to give (*R*)-ethyl 3-(tert-butoxycarbonylamino)-4-(2',5'-dichlorobiphenyl-4-yl)butanoate (1.09 g); HPLC retention time = 1.50 minutes (condition B); MS (ES+) = 352.00 (m-BOC+2; 100%); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, *J*= 7.1 Hz, 3 H) 1.41 (s, 9 H) 2.45 – 2.58 (m, 2 H) 2.85 – 3.00 (m, 2 H) 4.17 (t, *J* = 7.1 Hz, 2 H) 4.20 (br s, 1 H) 5.06 – 5.08 (m, 1 H) 7.23 – 7.28 (m, 3 H) 7.31 – 7.40 (m, 4 H).

Intermediate 20: Synthesis of (*R*)-3-amino-4-(3'-chlorobiphenyl-4-yl)butanoic acid hydrochloride



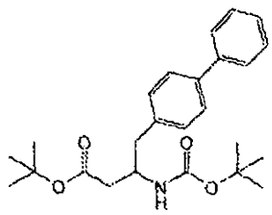
A solution of (*R*)-benzyl 3-(tert-butoxycarbonylamino)-4-(3'-chlorobiphenyl-4-yl)butanoate (152 mg, 0.317 mmol) and 1 M aqueous NaOH (1.583 ml, 1.583 mmol) in a mixed solvent of MeOH (0.3 ml) and THF (3 ml) is allowed to stir for 2 hours. The reaction is quenched with 1M aqueous HCl (2.5 ml). The products are extracted with EtOAc. The organic layer is dried over Na_2SO_4, filtered, and concentrated to give crude.
To the crude, a solution of 4 M HCl in 1,4-dioxane (1.583 ml, 6.33 mmol) is added. After stirring for 1 h, the precipitated solid is collected, and dried under reduced pressure to give (*R*)-3-amino-4-(3'-chlorobiphenyl-4-yl)butanoic acid hydrochloride (60.2 mg) as a white solid; HPLC retention time = 0.52 minutes (condition B); MS (m+1) = 290.22; 1H NMR (400 MHz, CD_3OD) δ ppm 2.58 - 2.74 (m, 2 H) 2.99 – 3.11 (m, 2 H) 3.80 – 3.85 (m, 1 H) 7.34 - 7.45 (m, 4 H) 7.54 - 7.57 (m, 1 H) 7.62 - 7.65 (m, 3 H).

Intermediate 21: Synthesis of a mixture of 1-(2-(benzyloxy)-2-oxoethyl)cyclopentanecarboxylic acid and 2-(1-(benzyloxycarbonyl)cyclopentyl)acetic acid



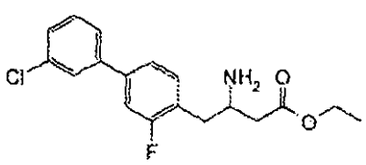
A solution of 2-oxaspiro[4.4]nonane-1,3-dione (3 g, 19.46 mmol) and benzyl alcohol (2.023 ml, 19.46 mmol) in toluene (2 ml) is allowed to stir at 100 °C for 19 hours. The reaction mixture is cooled to ambient temperature and concentrated to give 6:1 mixture of 1-(2-(benzyloxy)-2-oxoethyl)cyclopentanecarboxylic acid and 2-(1-(benzyloxycarbonyl)cyclopentyl)acetic acid (4.89 g); 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.60 - 1.78 (m, 6 H) 2.19 – 2.24 (m, 2 H) 2.75 (s, 2 H) 5.11 (s, 2 H, major isomer) 5.13 (s, 2 H, minor isomer) 7.30 – 7.37 (m, 5 H).

Intermediate 22: Synthesis of tert-butyl 4-(biphenyl-4-yl)-3-(tert-butoxycarbonylamino)butanoate



A solution of 4-(biphenyl-4-yl)-3-(tert-butoxycarbonylamino)butanoic acid (250 mg, 0.703 mmol), tBuOH (0.135 ml, 1.407 mmol), EDCI (270 mg, 1.407 mmol) and 4-dimethylaminopyridine (86.0 mg, 0.704 mmol) in DCM (7 ml) is allowed to stir at room temperature under nitrogen for 62 hours. The reaction is quenched with water, and the organic layer is separated and concentrated. The residue is purified by flash column chromatography on silica gel to give tert-butyl 4-(biphenyl-4-yl)-3-(tert-butoxycarbonylamino)butanoate (110 mg) ; HPLC retention time = 1.77 minutes (condition B); MS (ES+) = 412.1 (m+1) 300.0 (m-tBux2+3; 100%); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.41 (s, 9 H) 1.47 (s, 9 H) 2.36 (A of ABX, J_{ab} = 15.5 Hz, J_{ax} = 6.2 Hz, 1 H) 2.44 (B of ABX, J_{ab} = 15.5 Hz, J_{bx} = 5.6 Hz) 2.82 – 2.94 (m, 2 H) 4.11 – 4.17 (m, 1 H) 5.08 – 5.10 (m, 1 H) 7.25 - 7.34 (m, 3H) 7.41 – 7.44 (m, 2 H) 7.51-7.58 (m, 4 H).

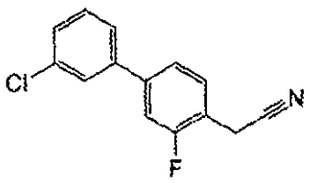
Intermediate 23: Synthesis of ethyl 3-amino-4-(3'-chloro-3-fluorobiphenyl-4-yl)butanoate



A suspension of zinc (479 mg, 7.33 mmol) and 1,2-dibromoethane (0.032 ml, 0.366 mmol) in THF (8 ml) is heated at 70 °C under nitrogen then a few drops of ethyl bromoacetate is added. After stirring for 20 min, a solution of 2-(3'-chloro-3-fluorobiphenyl-4-yl)acetonitrile (300 mg, 1.221 mmol) in THF (2 ml) is added in one portion. The remaining bromoacetate is added dropwise over 50 min (total amount of ethyl bromoacetate: 4.88 mmol). After stirring for 15 min at the same temperature, the reaction mixture is cooled to ambient temperature. To the reaction mixture, sodium triacetoxyborohydride (2588 mg, 12.22 mmol) and AcOH (8 ml) are added. The reaction mixture is allowed to stir for 13 hours, and concentrated to give

crude. The crude is diluted with EtOAc, and 2M aqueous Na_2CO_3 is added to be pH of 10. The products are extracted with EtOAc. The organic layer is dried over K2CO3, filtered, and concentrated to give crude. The resulting residue is purified by preparative HPLC using a gradient of 20% MeCN/water (0.1% NH_4OH) to 100% MeCN to give ethyl 3-amino-4-(3'-chloro-3-fluorobiphenyl-4-yl)butanoate (148 mg) as orange oil; HPLC retention time = 0.85 minutes (condition B); MS (m+1) = 336.13; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.27 (t, *J* = 7.1 Hz, 3 H) 2.36 (A of ABX, J_{ab} = 15.9 Hz, J_{ax} = 8.8 Hz, 1 H) 2.52 (B of ABX, J_{ab} = 15.9 Hz, J_{bx} = 4.0 Hz, 1 H) 2.71 – 2.76 (m, 1 H) 2.82 – 2.87 (m, 1 H) 3.51 – 3.57 (m, 1 H) 4.15 (d, *J* = 7.1 Hz, 2 H) 7.24 – 7.39 (m, 5 H) 7.42 – 7.44 (m, 1 H) 7.54 – 7.55 (m, 1 H).

Intermediate 24: Synthesis of 2-(3'-chloro-3-fluorobiphenyl-4-yl)acetonitrile



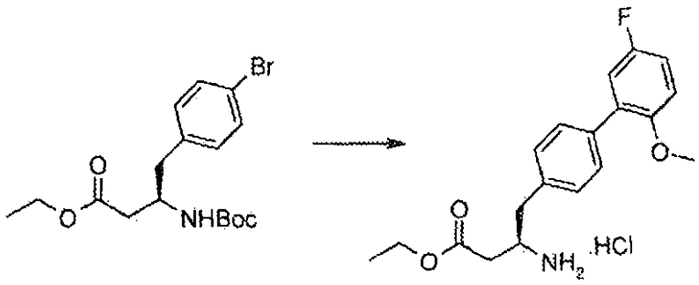
A suspension of 4-bromo-2-fluorobenzyl cyanide (3.50 g, 16.35 mmol), 3-chlorobenzeneboronic acid (2.68 g, 17.17 mmol), $Pd(OAc)_2$ (0.110 g, 0.491 mmol), K_2CO_3 (5.65 g, 40.9 mmol) and tetrabutylammonium bromide (5.80 g, 17.99 mmol) in water (14 ml) is allowed to stir under nitrogen at 70 °C for 1 hour. The reaction mixture is cooled to room temperature, and diluted with EtOAc. The two phases are separated. The organic layer is washed with brine, dried over $MgSO_4$, filtered and concentrated. The obtained residue is purified by silica gel flash column chromatography (heptane/EtOAc = 100:0 to 70:30) to give 2-(3'-chloro-3-fluorobiphenyl-4-yl)acetonitrile (3.52 g); HPLC retention time = 1.17 minutes (condition B); 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 3.81 (s, 2 H) 7.29 – 7.45 (m, 5 H) 7.50 – 7.55 (m, 2 H).

Intermediate 25: (R)-tert-butyl 4-(1-(4-bromophenyl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoate



To a solution of 4-tert-butoxy-4-oxobutanoic acid (2.38 g, 13.64 mmol) in DMF (30 mL) and DCM (30 mL) is added (R)-ethyl 3-amino-4-(4-bromophenyl)butanoate hydrochloride (4 g, 12.4 mmol), HATU (5.19 g, 13.64 mmol), and TEA (6.91 mL, 49.6 mmol). After stirring at room temperature for 2 hours, the reaction is quenched with H_2O, and the crude is diluted with EtOAc, the organic layer is washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give (R)-tert-butyl 4-(1-(4-bromophenyl)-4-ethoxy-4-oxobutan-2-ylamino)-4-oxobutanoate (4.0 g). HPLC retention time = 1.70 minutes (condition A); MS (m+1) = 444.1.

Intermediate 26: (R)-3-amino-4-(5'-fluoro-2'-methoxy-biphenyl-4-yl)-butyric acid ethyl ester hydrochloride salt

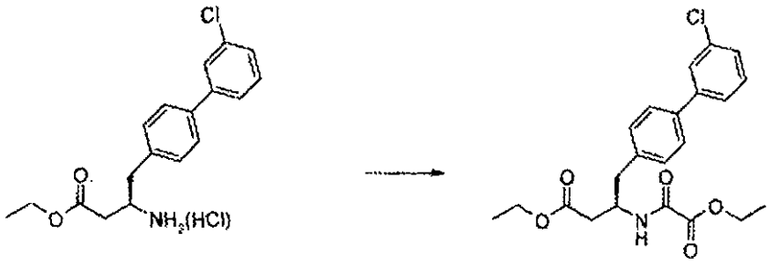


To a solution of (R)-ethyl 4-(4-bromophenyl)-3-(tert-butoxycarbonylamino)butanoate, (3.12 g, 8.08 mmol), and 5-fluoro-2-methoxyphenylboronic acid (2.2 g, 12.93 mmol) in toluene (52 mL) and is added $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (0.66 g, 0.81 mmol) and 2M aq. Na_2CO_3 (8.1 mL, 16.16 mmol). After stirring at 95 °C under nitrogen for 4 hours, the solution is cooled to ambient temperature and then quenched with ice water. The crude is diluted with ethyl acetate. The organic layer is washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue is purified by flash column chromatography on silica gel (eluent: heptane/EtOAc = 100:0 to 50:50) to give (R)-ethyl 3-(tert-butoxycarbonylamino)-4-(5'-fluoro-2'-methoxybiphenyl-4-yl)butanoate (2.86 g). HPLC retention time = 1.80 minutes (condition A); MS (m+1) = 432.2; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.31 (t, *J*=7.1 Hz, 3 H) 1.45 (s, 9 H) 2.45 - 2.65 (m, 2 H) 2.83 - 2.94 (m, 1 H) 2.94 - 3.09 (m, 1 H) 3.80 (s, 3 H) 4.20 (q, *J*=7.2 Hz, 2 H) 4.24 - 4.33 (m, 1 H) 5.11 (br. s., 1 H) 6.90 - 6.96 (m, 1 H) 7.00 (dd, *J*=7.8, 3.3 Hz, 1 H) 7.06 (dd, *J*=9.2, 3.2 Hz, 1 H) 7.27 (d, *J*=7.8 Hz, 2 H) 7.49 (d, *J*=7.8 Hz, 2 H)

A solution of (R)-ethyl 3-(tert-butoxycarbonylamino)-4-(5'-fluoro-2'-methoxybiphenyl-4-yl)butanoate, (2.86 g, 6.62 mmol) in 4M HCl in 1,4-dioxane (33.1 ml, 132 mmol) is stirred at

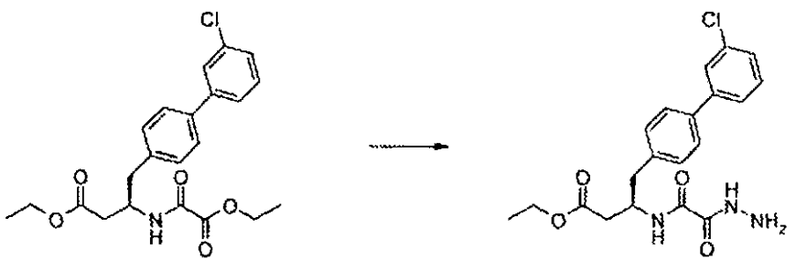
room temperature. After stirring for 1 hour, the reaction mixture is concentrated under reduced pressure to give (R)-ethyl 3-amino-4-(5'-fluoro-2'-methoxybiphenyl-4-yl)butanoate hydrochloride salt (2.44 g). HPLC retention time = 1.46 minutes (condition A); MS (m+1) = 332.3; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.15 (t, *J*=6.4 Hz, 3 H) 2.66 - 2.77 (m, 1 H) 2.78 - 2.91 (m, 1 H) 2.94 - 3.10 (m, 1 H) 3.42 - 3.53 (m, 1 H) 3.67 (s, 3 H) 3.83 - 3.96 (m, 1 H) 4.07 (q, *J*=6.8 Hz, 2 H) 6.77 - 6.84 (m, 1 H) 6.87 - 6.96 (m, 2 H) 7.23 (d, *J*=7.1 Hz, 2 H) 7.38 (d, *J*=7.1 Hz, 2 H) 8.64 (br. s., 2 H)

Intermediate 27: (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-ethoxy-2-oxoacetamido)butanoate



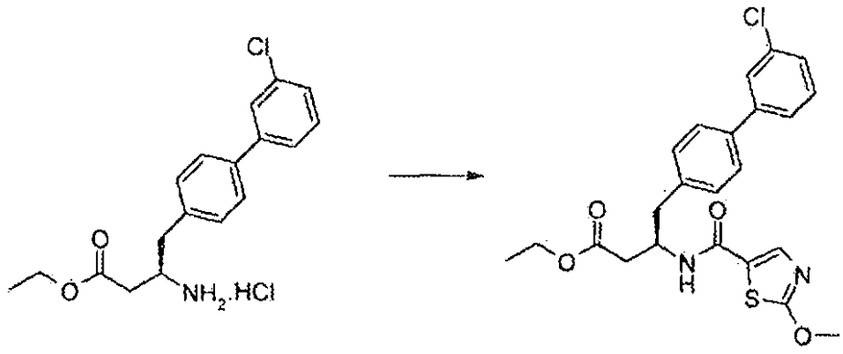
To a solution of (R)-ethyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride (500 mg, 1.57 mmol) in DMF (11 mL) is added TEA (0.23 mL, 1.65 mmol) and ethyl 2-chloro-2-oxoacetate (0.18 mL, 1.57 mmol) at room temperature. After stirring for 1 hour at room temperature, the reaction is quenched with H_2O, and the crude is diluted with EtOAc. The organic layer is washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue is purified by flash column chromatography on silica gel (eluent: heptane/EtOAc = 70:30 to 50:50) to give (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-ethoxy-2-oxoacetamido)butanoate (550 mg). HPLC retention time = 1.88 minutes (condition A); MS (m+1) = 418.3

Intermediate 28: (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-hydrazinyl-2-oxoacetamido)butanoate



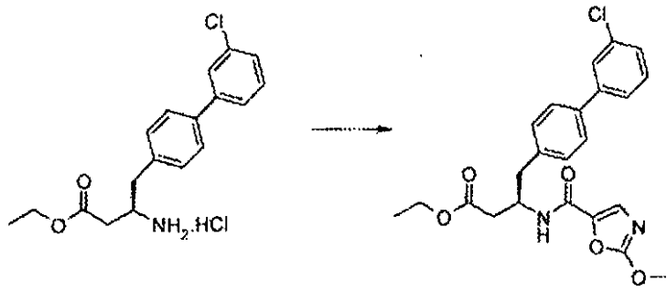
To a solution of (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-ethoxy-2-oxoacetamido)butanoate (450 mg, 1.08 mmol) in MeOH (24 mL) is added a solution of 50% wt hydrazine (0.068 ml, 1.08 mmol) in MeOH (10 mL) at -20°C. After stirring for 18 hours at room temperature, the reaction mixture is concentrated under reduced pressure to give (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-hydrazinyl-2-oxoacetamido)butanoate (412 mg). HPLC retention time = 1.76 minutes (condition A); MS (m+1) = 404.1

Intermediate 29: (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-methoxythiazole-5-carboxamido)butanoate



To a solution of 2-methoxythiazole-5-carboxylic acid (80 mg, 0.50 mmol) and (*R*)-ethyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride (160 mg, 0.45 mmol) in DMF (5 mL) is added HATU (207 mg, 0.55 mmol) and TEA (276 mg, 2.73 mmol). The crude is stirred at room temperature for 2 hrs. The crude is neutralized with 1 N HCl and diluted in water and EtOAc. The organic layer is washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude is purified via flash chromatography using 30% EtOAc/heptane to 70% EtOAc/heptane to give (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-methoxythiazole-5-carboxamido)butanoate (170 mg). HPLC retention time = 1.97 minutes (condition D); MS (m+1) = 459.1. 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 (t, *J*=7.1 Hz, 3 H) 2.49 - 2.69 (m, 2 H) 2.93 (dd, *J*=13.6, 8.1 Hz, 1 H) 3.10 (dd, *J*=13.5, 6.2 Hz, 1 H) 4.09 (s, 3 H) 4.00-4.15 (m, 2 H) 4.53 - 4.69 (m, 1 H) 6.78 (d, *J*=8.6 Hz, 1 H) 7.25 - 7.32 (m, 3 H) 7.35 (t, *J*=7.71 Hz, 1 H) 7.44 (dt, *J*=7.6, 1.5 Hz, 1 H) 7.48 - 7.54 (m, 3 H) 7.55 (t, *J*=1.8 Hz, 1 H).

Intermediate 30: (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-methoxyoxazole-5-carboxamido)butanoate



To a solution of 2-methoxyoxazole-5-carboxylic acid, intermediate 16, (98 mg, 0.69 mmol) and (*R*)-ethyl 3-amino-4-(3'-chlorobiphenyl-4-yl)butanoate hydrochloride (210 mg, 0.57 mmol) in DMF (10 mL) and CH_2Cl_2 (4 mL) is added HATU (272 mg, 0.72 mmol) and TEA (0.50 mL, 3.58 mmol). The crude is stirred at room temperature for 2 hrs. The crude is quenched with water and diluted in EtOAc. The organic layer is washed with water 3X, brine, dried over $MgSO_4$, filtered, and concentrated. The crude is purified via flash chromatography using 30% EtOAc/heptane to 70% EtOAc/heptane to give (R)-ethyl 4-(3'-chlorobiphenyl-4-yl)-3-(2-methoxyoxazole-5-carboxamido)butanoate (122 mg). HPLC retention time = 1.89 minutes (condition A); MS (m+1) = 443.2; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (t, *J*=7.1 Hz, 3 H), 2.52 - 2.66 (m, 2 H), 2.94 (dd, 1 H), 3.08 (dd, *J*=13.6, 6.3 Hz, 1 H), 4.12 (s, 3 H), 4.14 - 4.23 (m, 2 H), 4.60 - 4.71 (m, 1 H), 6.81 (d, *J*=8.8 Hz, 1 H), 7.25 - 7.32 (m, 3 H), 7.35 (t, *J*=7.7 Hz, 1 H), 7.42 (s, 1 H), 7.43 - 7.47 (m, 1 H), 7.48 - 7.54 (m, 2 H), 7.55 (t, *J*=1.6 Hz, 1 H).

Intermediate 31: 6-(methylsulfonamido)nicotinic acid



To a solution of methyl 6-aminonicotinate (1.0 g, 6.57 mmol) in CH_2Cl_2 (50 mL) with TEA (0.96 mL, 6.90 mmol) cooled in an ice bath is added MsCl (0.54 mL, 6.90 mmol) slowly. The crude is allowed to stir at room temperature for 2 hrs. The crude is then concentrated. The crude is dissolved in MeOH (20 mL) and to the crude is added 1 N NaOH (30 mL, 30 mmol). The crude is stirred at room temperature for 18 hrs. The crude is quenched with 1N HCl (32 mL, 32 mmol). The crude is concentrated to remove MeOH and some water is removed as

well. The crude is diluted in CH_2Cl_2 and basified with 1 N NaOH (30 mL). The aq. layer is extracted with CH_2Cl_2. The aq. layer is acidified with concentrated HCl to bring the PH to 1 via PH paper indicator. The crude is diluted in EtOAc and the aq. layer is extracted with EtOAc. The combined organic layer is washed with brine, dried over MgSO4, filtered, and concentrated to give 6-(methylsulfonamido)nicotinic acid (421mg) as a yellow solid. HPLC retention time = 0.40 minutes (condition D); MS (m+1) = 217.2.

Intermediate 32: 2-methoxyoxazole-5-carboxylic acid



To a solution of ethyl 2-chlorooxazole-5-carboxylate (510 mg, 2.90 mmol) in anhdryous MeCN (10 mL) and anhydrous MeOH (10 mL) is added NaOMe (628 mg, 11.62 mmol). The crude is stirred at reflux for 2 hrs. To this crude is added additional MeOH. The crude is refluxed for another 4 hrs. The crude is concentrated and is redissolved in MeOH (10 mL). To this crude is added 1 N NaOH (10 ml). The crude is stirred at room temperature for 3 hrs. The crude is quenched with concentrated HCl, PH adjusted to 7 via PH paper indicator. The crude is concentrated and diluted in water. The aq. layer is acidified with concentrated HCl and diluted in EtOAc. The organic layer is washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to give2-methoxyoxazole-5-carboxylic acid (290 mg). HPLC retention time = 0.58 minutes (condition D); MS (m+1) = 144.0.

Intermediate 33: ethyl 5-oxo-4,5-dihydro-1,2,4-oxadiazole-3-carboxylate



To a solution of ethyl 2-(hydroxyamino)-2-iminoacetate (2 g, 15.14 mmol) in dioxane (15.00 mL) is added CDI (2.7 g, 16.65 mmol) and DBU (2.5 ml, 16.65 mmol) at room temperature. After stirring for 1 hour at 80°C, the reaction is quenched with 1N HCl, and the crude is diluted with EtOAc. The organic layer is washed with brine, dried over Na_2SO_4, filtered and

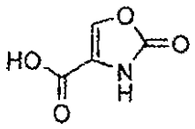
concentrated under reduced pressure to give ethyl 5-oxo-4,5-dihydro-1,2,4-oxadiazole-3-carboxylate (2.4 g). HPLC retention time = 0.72 minutes (condition D); MS 159.1 (M+1).

Intermediate 34: 5-oxo-4,5-dihydro-1,2,4-oxadiazole-3-carboxylic acid



To a solution of crude ethyl 5-oxo-4,5-dihydro-1,2,4-oxadiazole-3-carboxylate (2.4 g, 15.14 mmol) in MeOH (2 mL) is added aqueous 1N NaOH (4 mL, 4 mmol) at room temperature. After stirring for 5 hours at room temperature the reaction is quenched with 1N HCl (5 mL, 5 mmol), the crude is concentrated under reduced pressure to remove MeOH. The crude is diluted with EtOAc, the organic layer is washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 5-oxo-4,5-dihydro-1,2,4-oxadiazole-3-carboxylic acid (1.9 g).

Intermediate 35: 2-oxo-2,3-dihydrooxazole-4-carboxylic acid



This intermediate is prepared according to: Okonya, J. F.; Hoffman, R. V.; Johnson, M. C.; *J. Org. Chem.* **2002**, 67, 1102-1108.

Intermediate 36: 3-hydroxyisothiazole-5-carboxylic acid



To a solution of methyl 3-hydroxyisothiazole-5-carboxylate (300 mg, 1.73 mmol) in MeOH (2 mL) is added 1N NaOH (6 mL, 6 mmol). After stirring at room temperature for 2 hours, the crude is concentrated under reduced pressure to remove MeOH and is diluted with EtOAc. The organic layer is washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 3-hydroxyisothiazole-5-carboxylic acid (250 mg).

Intermediate 37: ethyl 2-vinyloxazole-5-carboxylate



To a solution of tributyl(vinyl)stannane (1.1 mL, 3.83 mmol) and ethyl 2-chlorooxazole-5-carboxylate (546 mg, 3.11 mmol) in dioxane (37 mL) is added $Pd(PPh_3)_2Cl_2$ (222 mg, 0.32 mmol) at room temperature. After stirring at 100 °C under nitrogen for 4 hours, the solution is cooled to ambient temperature and then quenched with H_2O. The crude is diluted with EtOAc, the organic layer is washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue is purified by flash column chromatography (eluent: heptane/EtOAc = 90:10 to 80:20) to give ethyl 2-vinyloxazole-5-carboxylate (470 mg). HPLC retention time = 0.39 minutes (condition B); MS (m+1) = 168.2; 1H NMR (400 MHz, CD_3OD) δ ppm 1.38 (t, *J*=7.1 Hz, 3 H) 4.38 (q, *J*=7.2 Hz, 2 H) 5.88 (d, *J*=11.4 Hz, 1 H) 6.39 (d, *J*=17.7 Hz, 1 H) 6.69 (dd, *J*=17.6, 11.2 Hz, 1 H) 7.83 (s, 1 H)

Intermediate 38: ethyl 2-ethyloxazole-5-carboxylate



To a solution of ethyl 2-vinyloxazole-5-carboxylate (470 mg, 2.81 mmol) in MeOH (7 mL) is added 10% wt. Pd/C (100 mg, 0.094 mmol) at room temperature. After stirring at room temperature under a balloon of hydrogen for 1 hour, the crude is filtered to remove Pd/C. The filtrate is collected and concentrated to give ethyl 2-ethyloxazole-5-carboxylate (470 mg). HPLC retention time = 1.09 minutes (condition A); MS (m+1) = 170.3; 1H NMR (400 MHz, CD_3OD) δ ppm 1.35 (t, *J*=7.6 Hz, 3 H) 1.36 (t, *J*=7.2 Hz, 3 H) 2.87 (q, *J*=7.7 Hz, 2 H) 4.35 (q, *J*=7.2 Hz, 2 H) 7.71 (s, 1 H)

Intermediate 39: 2-ethyloxazole-5-carboxylic acid



To a solution of 2-ethyloxazole-5-carboxylate (470 mg, 2.81 mmol) in MeOH (10 mL) is added 1N NaOH (6 mL, 6 mmol). After stirring at room temperature for 18 hours, the crude

is concentrated under reduced pressure to remove MeOH and is diluted with EtOAc. The organic layer is washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 2-ethyloxazole-5-carboxylic acid (244 mg). 1H NMR (400 MHz, CD_3OD) δ ppm 1.36 (t, *J*=7.7 Hz, 3 H) 2.89 (q, *J*=7.6 Hz, 2 H) 5.15 (br. s., 1 H) 7.69 (s, 1 H)

Intermediate 40: ethyl 2-vinylthiazole-5-carboxylate



To a solution of tributyl(vinyl)stannane (0.92 mL, 3.14 mmol) and ethyl 2-bromothiazole-5-carboxylate (0.38 mL, 2.54 mmol) in dioxane (33 mL) is added $Pd(PPh_3)_2Cl_2$ (182 mg, 0.26 mmol) at room temperature. After stirring at 100 °C under nitrogen for 4 hours, the solution is cooled to ambient temperature and then quenched with H_2O. The crude is diluted with EtOAc, the organic layer is washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue is purified by flash column chromatography on silica gel (eluent: heptane/EtOAc = 90:10 to 80:20) to give ethyl 2-vinylthiazole-5-carboxylate (418 mg). HPLC retention time = 0.45 minutes (condition B); MS (m+1) = 184.1; 1H NMR (400 MHz, CD_3OD) δ ppm 1.37 (t, *J*=7.2 Hz, 3 H) 4.35 (q, *J*=7.1 Hz, 2 H) 5.71 (d, *J*=10.9 Hz, 1 H) 6.24 (d, *J*=17.4 Hz, 1 H) 6.93 (dd, *J*=17.4, 10.9 Hz, 1 H) 8.29 (s, 1 H)

Intermediate 41: ethyl 2-ethylthiazole-5-carboxylate



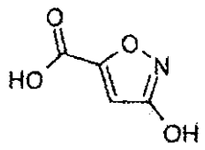
To a solution of ethyl 2-vinylthiazole-5-carboxylate (400 mg, 2.18 mmol) in MeOH (7 mL) is added 10% wt. Pd/C (267 mg, 0.25 mmol) at room temperature. After stirring at room temperature under a balloon of hydrogen for 1 hour, the crude is filtered to remove Pd/C. The filtrate is concentrated to give ethyl 2-ethylthiazole-5-carboxylate (404 mg). HPLC retention time = 0.60 minutes (condition B); MS (m+1) = 186.3; 1H NMR (400 MHz, CD_3OD) δ ppm 1.35 (t, *J*=7.3 Hz, 2 H) 1.39 (t, *J*=7.20 Hz, 2 H) 3.07 (q, *J*=7.58 Hz, 2 H) 4.35 (q, *J*=7.16 Hz, 2 H) 8.22 (s, 1 H)

Intermediate 42: 2-ethylthiazole-5-carboxylic acid



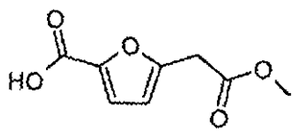
To a solution of ethyl 2-ethylthiazole-5-carboxylate (400 mg, 2.159 mmol) in MeOH (10 mL) is added 1N NaOH (6 mL, 6 mmol) After stirring at room temperature for 18 hours, the crude is concentrated under reduced pressure to remove MeOH. The crude is diluted with EtOAc, the organic layer is washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 2-ethylthiazole-5-carboxylic acid (282.4 mg). HPLC retention time = 0.78 minutes (condition D); MS (m+3) = 160.4; 1H NMR (400 MHz, CD_3OD) δ ppm 1.40 (t, *J*=7.6 Hz, 3 H) 3.07 (q, *J*=7.6 Hz, 2 H) 5.08 (br. s., 1 H) 8.20 (s, 1 H).

Intermediate 43: 3-Hydroxy-isoxazole-5-carboxylic acid



To a solution of 3-hydroxy-isoxazole-5-carboxylic acid methyl ester (286 mg, 2.0 mmol) in methanol (7 mL) is added 1N NaOH (4.0 mL, 4.0 mmol) and the mixture is stirred at room temperature for 18 hrs. The solvent is removed under reduced pressure and 4.0 mL of 1N HCl is added to the residue. The resulting solution is lyophilized to give the product which is used as is in subsequent reactions.

Intermediate 44: 5-Methoxycarbonylmethyl-furan-2-carboxylic acid

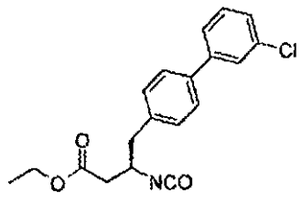


To a solution of 5-methoxycarbonylmethyl-furan-2-carboxylic acid methyl ester (250 mg, 1.26 mmol) in methanol (5 mL) is added 1N NaOH (2.78 mL, 2.78 mmol) and the mixture is stirred at room temperature for 18 hours. The solvent is removed under reduced pressure and 2.78 mL of 1N HCl is added to the residue. The resulting solution is lyophilized to give 5-carboxymethyl-furan-2-carboxylic acid.

Next, to a solution of the above diacid (220 mg, 1.29 mmol) in methanol (8 mL) is added Amberlyst-15 resin (50 mg) and the mixture is stirred at room temperature for 18 hours. The

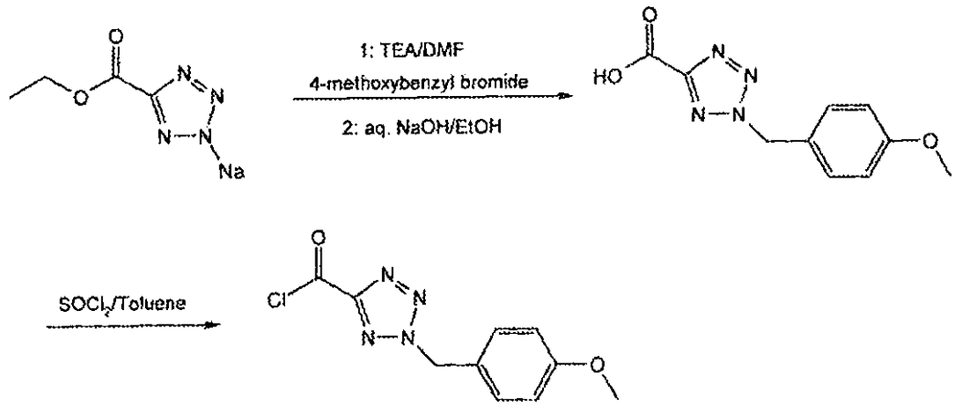
resin is filtered and the solvent is removed under reduced pressure to give the product which is used as is in subsequent reactions. 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 3.75 (s, 3H), 3.82 (s, 2H), 6.45 (d, J=3.54 Hz, 1H), 7.29 (d, J=3.54 Hz, 1H), 10.17 (s, broad, 1H).

Intermediate 45: (R)-4-(3'-Chloro-biphenyl-4-yl)-3-isocyanato-butyric acid ethyl ester



To a vigorously stirred mixture of 8% aqueous sodium bicarbonate (3 mL) and methylene chloride (3 mL) at 0 °C is added triphosgene (28.1 mg, 0.095 mmol) and the mixture is stirred at 0 °C for 5 minutes then Intermediate 17-1 (100 mg, 0.284 mmol) is added and stirring is continued for an additional 15 minutes. The organic layer is separated and dried over sodium sulfate. The solvent is removed under reduced pressure to give the title compound. This is used as is in subsequent reactions.

Intermediate 46: 2-(4-Methoxy-benzyl)-2H-tetrazole-5-carbonyl chloride

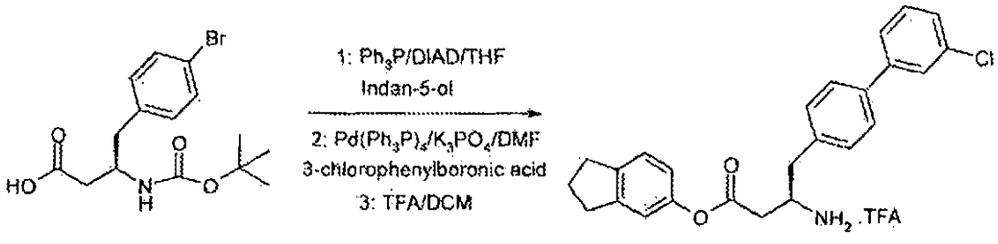


To a solution of 1H-tetrazole-5-carboxylic acid ethyl ester sodium salt (500 mg, 3.05 mmol) in DMF (5 ml) at room temperature is added 4-methoxybenzyl chloride (747 µl, 5.48 mmol) and TEA (1500 µl, 10.76 mmol). The reaction mixture is stirred at room temperature overnight. The reaction is added water and extracted with EtOAc. The combined organic layer is washed with brine and dried over anhydrous sodium sulfate, filtered and

concentrated under reduced pressure. The residue is purified by column chromatography (10% to 30% EtOAc/Heptane). To a solution of the purified residue in EtOH (2 ml) at room temperature is added NaOH (2 ml, 2.000 mmol) and the mixture is stirred at room temperature. After stirring for 1 hour, the mixture is concentrated under reduced pressure to remove EtOH and extracted with EtOAC after being acidified to pH <5. The combined organic layer is washed with brine and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2-(4-methoxy-benzyl)-2H-tetrazole-5 -carboxylic acid.

Next, to a mixture of 2-(4-methoxy-benzyl)-2H-tetrazole-5-carboxylic acid in Toluene (15 ml) at room temperature is added $SOCl_2$ (1 ml, 13.70 mmol) and the mixture is heated at 80 °C for 3 hr. The reaction mixture is concentrated under reduced pressure to give the crude product , which is used without further purification.

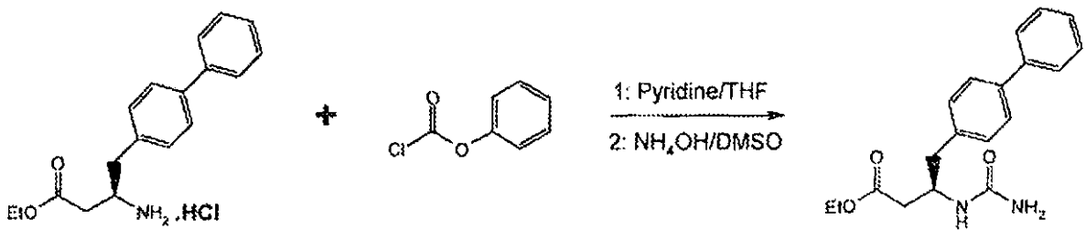
Intermediate 47: (R)-3-Amino-4-(3'-chloro-biphenyl-4-yl)-butyric acid indan-5-yl ester



To a suspension of boc-(R)-3-amino-4-(4-bromo-phenyl)-butanoic acid (500 mg, 1.396 mmol) in THF (12 ml) at room temperature is added 5-indanol (187 mg, 1.396 mmol) and Ph_3P (403 mg, 1.535 mmol). To the mixture at ice bath is added DIAD (0.326 ml, 1.675 mmol) and the mixture is stirred from ice bath to room temperature overnight. The reaction is concentrated under reduced pressure and purified by column chromatography (5% to 20% EtOAc/Heptane) to give 450 mg of solid. To a solution of the obtained solid (200 mg, 0.422 mmol) in DMF (5 ml) at room temperature is added 3-chlorophenylboronic acid (79 mg, 0.506 mmol), tripotassium phosphate (134 mg, 0.632 mmol) and $Pd(PPh_3)_4$ (48.7 mg, 0.042 mmol). The reaction is stirred at 100 °C overnight. The reaction is quenched by brine and is extracted with EtOAc. The combined organic layer is washed with brine and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography (5% to 30% EtOAc/Heptane). To the obtained residue (143 mg, 0.283 mmol) in DCM (1 ml) at room temperature is added TFA (1 mL, 12.98 mmol)

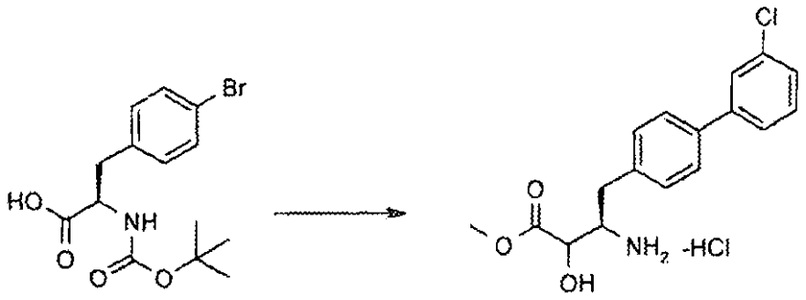
and the mixture is stirred at room temperature for 2 hours. The mixture is concentrated to give the crude salt which is used directly without further purification. HPLC retention time = 1.27 minutes (condition B); MS (m+1) = 406.

Intermediate 48: (R)-4-Biphenyl-4-yl-3-ureido-butyric acid ethyl ester



To a suspension of (R)-3-amino-4-biphenyl-4-yl-butyric acid ethyl ester (200 mg, 0.625 mmol) in THF (10 ml) at 0 °C was added phenyl chloroformate (0.087 ml, 0.688 mmol) and pyridine (0.126 ml, 1.563 mmol). The mixture is stirred at 0 °C for 5 min then is warmed up to room temperature. LCMS monitored the reaction until it is complete. The reaction is extracted with EtOAc. The combined organic layer is washed with 1N HCl, H_2O, sat. aq. $NaHCO_3$ and brine and dried over anhydrous sodium sulfate, filtered and concentrated to give the crude residue.
Next, to a solution of the obtained residue (0.252 g, 0.625 mmol) in DMSO (1.5 ml) at room temperature is added ammonium hydroxide (0.027 ml, 0.688 mmol). The reaction is stirred at room temperature. 30 min LCMS showed small desired product with big starting material so more ammonium hydroxide is added and the reaction is stirred at room temperature overnight until the reaction is complete. The reaction is extracted with EtOAc. The combined organic layer is washed with H_2O, 1N HCl, H_2O, 1 N NaOH and brine and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography (2% to 6% EtOH/DCM) to give (R)-4-biphenyl-4-yl-3-ureido-butyric acid ethyl ester (169 mg). HPLC retention time = 1.04 minutes (condition B); MS (m+1) = 327.

Intermediate 49: (R)-3-amino-4-(3'-chloro-biphenyl-4-yl)-2-hydroxy-butyric acid methyl ester hydrochloride



(R)-3-(4-Bromo-phenyl)-2-tert-butoxycarbonylamino-propionic acid (4.0 g, 11.6 mmol), 3-chlorophenylboronic acid (2.36 g, 15.11 mmol), $Pd(PPh_3)_4$ (0.067 g, 0.058 mmol) and 2M Na_2CO_3 aqueous solution (8.0 mL) are refluxed in 1,2-dimethoxyethane (70 mL) for 2.5 h under N_2 atomosphere. After cooling to room temperature, the reaction mixture is diluted with EtOAc and washed with 1M HCl and brine. The organic layer is dried over Na_2SO_4 and cocentrated. The residue is purified by flash column chromatography (silica gel, DCM/10%MeOH in DCM = 100:0 to 0:100),to give (R)-2-tert-butoxycarbonylamino-3-(3'-chloro-biphenyl-4-yl)-propionic acid (containing inpurities). HPLC retention time = 1.56 minutes (condition A): MS (m+1) = 376.

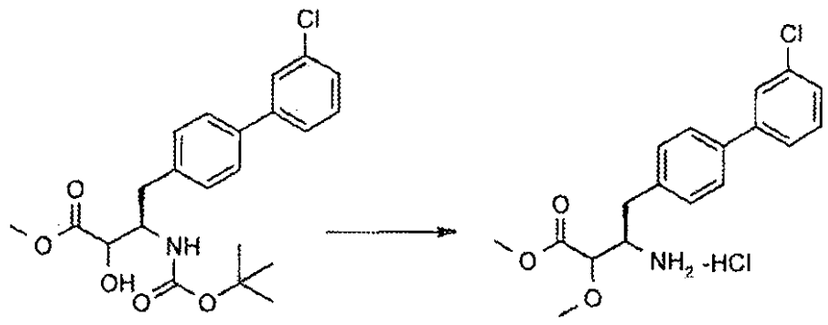
This is dissolved in 1, 2-dimethoxyethane (40 mL) and Et_3N (1.46 mL, 10.5 mmol) and ethyl chloroformate (1.00 mL, 10.5 mmol) are added. After being stirred at room temperature for 0.5h, the resultant precipitate is removed by filtration. To the filtrate is slowly added $NaBH_4$ (0.44 g, 11.6 mmol) in H_2O (5 mL). After being stirred for 2 h, the reaction mixture is diluted with EtOAc and washed with H_2O and brine. The organic layer is dried over Na_2SO_4, concentrated and purified by flash column chromatography (silica gel, eluent; heptane/EtOAc = 100:0 to 0:100) to give [(R)-2-(3'-chloro-biphenyl-4-yl)-1-hydroxymethyl-ethyl]-carbamic acid tert-butyl ester (2.8 g). HPLC retention time = 1.26 minutes (condition A): MS (m+1-Boc) = 262. 1H-NMR (400 MHz, DMSO-d6) δ ppm 1.43 (s, 9 H), 2.90 (d, 2 H, *J* = 7.33 Hz), 3.60 (dd, 1 H, *J* = 5.05, 10.86 Hz), 3.72 (dd, 1 H, *J* = 3.79, 11.12 Hz), 3.91 (bs, 1 H), 4.75 (bs, 1 H), 7.29-7.34 (m, 3 H), 7.37 (t, 1 H, *J* = 7.83 Hz), 7.44-7.48 (m, 1 H), 7.51 (d, 2 H, *J* = 8.08 Hz), 7.57 (t, 1 H, *J* = 1.77 Hz).

Next, to a solution of [(R)-2-(3'-chloro-biphenyl-4-yl)-1-hydroxymethyl-ethyl]-carbamic acid tert-butyl ester (2.0 g, 5.53 mmol) in DCM (30 mL) is added Dess-Martin periodinane (2.81 g, 6.63 mmol). After being stirred at room temperature for 2 h, the reaction mixture is diluted with EtOAc and washed with saturated $NaHCO_3$ aqueous solution and brine. The organic layer is dried over Na_2SO_4 and concentrated. The residue is purified by flash column

chromatography (silica gel, eluent; heptane/EtOAc = 100:0 to 0:100) to give [(R)-2-(3'-chloro-biphenyl-4-yl)-1-formyl-ethyl]-carbamic acid tert-butyl ester (1.05 g). HPLC retention time = 1.27 minutes (condition A): MS (m+1) = 360.
This is dissolved in MeOH (20 mL) and AcOH (0.199 mL, 3.47 mmol). To this solution KCN (0.226 g, 3.47 mmol) in H_2O (4 mL) is slowly addd. After being stirred at room temperature overnight, the reaction mixture is diluted with EtOAc and washed with saturated $NaHCO_3$ aqueous solution, H_2O and brine. The organic layer is dried over Na_2SO_4 and concentrated. This is treated with 4M HCl in dioxane (20 mL) and MeOH (10 mL) at room temperature. After being stirred overnight, the reaction mixture is concentrated. The residue is dissolved in MeOH and treated with $SOCl_2$ (0.211 mL, 2.89 mmol). After being stirred at 50°C for 5 h, the reaction mixture is concentrated to dryness. The residue is dissolved in THF (10 mL) and treated with saturated $NaHCO_3$ aqueous solution (5 mL) and Boc_2O (0.631 g, 2.89 mmol). After being stirred at room temperature for 2 h, the reaciton mixutre is diluted with EtOAc and washed with brine. The organic layer is dried over $MgSO_4$ and concentrated. The residue is purified by flash column chromatography (silica gel, eluent; heptane/EtOAc = 100:0 to 0:100) to give (R)-3-tert-butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-2-hydroxy-butyric acid methyl ester (0.61 g). HPLC retention time = 1.01, 1.06 minutes (condition B): MS (m+1-Boc) = 320. 1H-NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (s, 9 H), 2.77-3.05 (m, 2 H), 3.63 (s, 0.7 H), 3.77 (s, 2.3 H), 4.11 (s, 0.8 H), 4.25-4.40 (m, 1.2 H), 4.78-4.95 (m, 1 H), 7.27-7.40 (m, 4 H), 7.42-7.58 (m, 4 H).

(R)-3-tert-butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-2-hydroxy-butyric acid methyl ester (113 mg, 0.269 mmol) is treated with 4M HCl in dioxane (2 mL). After being stirred at room temperature for 1h, the reaction mixture is concnetrated. The residue is used for a next step without further purification. HPLC retention time = 1.22, 1.29 minutes (condition A): MS (m+1) = 320.

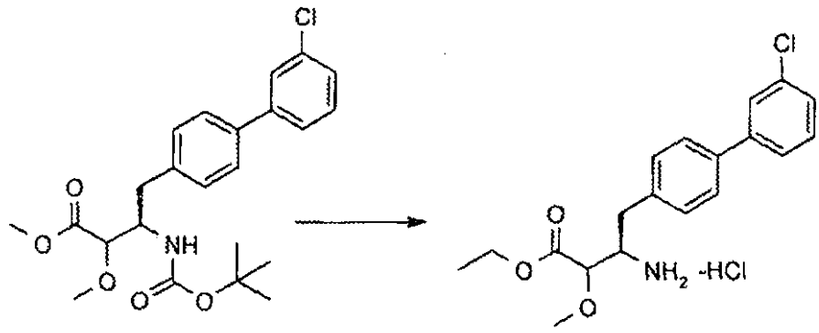
Intermediate 50: (R)-3-amino-4-(3'-chloro-biphenyl-4-yl)-2-methoxy-butyric acid methyl ester hydrochloride



To a solution of (R)-3-tert-butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-2-hydroxy-butyric acid methyl ester (610 mg, 1.45 mmol) in CH_3CN (20 mL) are added iodomethane (0.545 mL, 8.72 mmol) and silver oxide (1.35 g, 5.81 mmol). After being stirred at room temperature for 16 h, additional iodomethane (0.545 mL, 8.72 mmol) and silver oxide (1.35 g, 5.81 mmol) are added and stirred for 3 days. The reaction mixture is filtered through celite pad and the filtrate is washed with brine. The organic layer is dried over $MgSO_4$ and concnetrated. The residue is purified by flash column chromatography (silica gel, eluent; heptane/EtOAc = 100:0 to 0:100) to give (R)-3-tert-butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-2-methoxy-butyric acid methyl ester (500 mg). HPLC retention time = 1.20, 1.25 minutes (condition B): MS (m+1-Boc) = 334. 1H-NMR (400 MHz, $CDCl_3$) δ ppm 1.37, 1.41 (s, 9 H), 2.72-3.03 (m, 2 H), 3.43, 3.71 (s, 3H), 3.63-3.82 (m, 1 H), 4.27-4.41 (m, 1 H), 4.68-5.04 (m, 1 H), 7.28-7.40 (m, 4 H), 7.41-7.61 (m, 4 H).

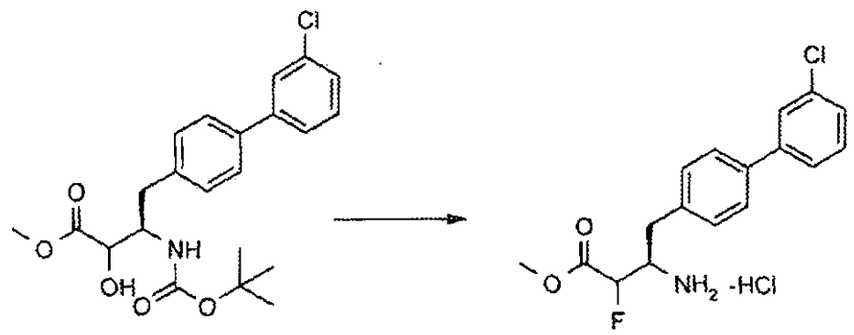
(R)-3-tert-butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-2-methoxy-butyric acid methyl ester (200 mg, 0.461 mmol) is treated with 4M HCl in dioxane (3 mL). After being stirred at room temperature for 1h, the reaction mixture is concnetrated. The residue is used for a next step without further purification. HPLC retention time = 1.26, 1.33 minutes (condition A): MS (m+1) = 334.

Intermediate 51: (R)-3-amino-4-(3'-chloro-biphenyl-4-yl)-2-methoxy-butyric acid ethyl ester hydrochloride



To a solution of (R)-3-amino-4-(3'-chloro-biphenyl-4-yl)-2-methoxy-butyric acid methyl ester (500 mg, 1.15 mmol) in MeOH (5mL) is added 2M NaOH aqueous solution (5 mL). After being stirred at room temperature for 2h, the reaction mixture is acidified with 2M HCl and extracted with EtOAc. The organic layer is dried over Na_2SO_4 and concentrated. The residue is dissolved in EtOH (5 mL) and treated with $SOCl_2$ (0.252 mL, 3.26 mmol). After being stirred at 55°C, the reaction mixture was cocentrated. The residue is used for a next step withour further purification. HPLC retention time = 1.49 minutes (condition A): MS (m+1) = 348.2

Intermediate 52: (R)-3-Amino-4-(3'-chloro-biphenyl-4-yl)-2-fluoro-butyric acid methyl ester hydrochloride

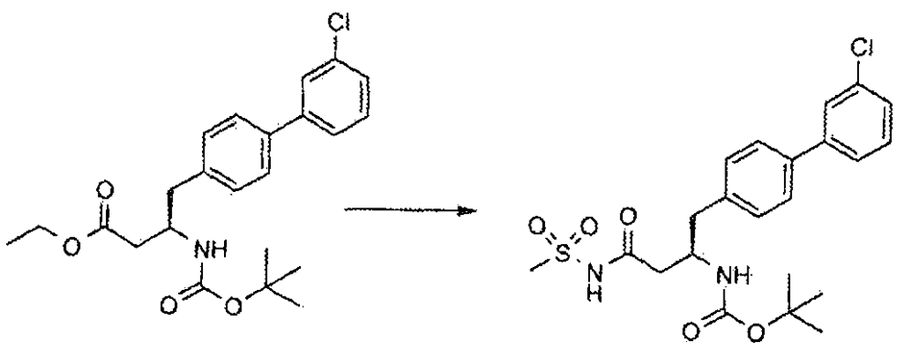


To a solution of (R)-3-tert-butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-2-hydroxy-butyric acid methyl ester (220 mg, 0.524 mmol) is added DAST (0.083 mL, 0.629 mmol) at 0°C. The reaction mixture is gradually warmed to room temperature and stirred for 1 h. Additional DAST (0.083 mL, 0.629 mmol) is added and stirred at room temperature for 2 h. The reaction mixture is diluted with EtOAc and washed with saturated $NaHCO_3$ aqueous solution and brine. The organic layer is dried over Na_2SO_4 and concentrated. The residue is purified by flash column chromatography (silica gel, eluent; heptane/EtOAc = 100:0 to 0:100) to give

(R)-3-tert-butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-2-fluoro-butyric acid methyl ester (63 mg). HPLC retention time = 1.36 minutes (condition B): MS (m+1-Boc) = 322.1H-NMR (400 MHz, $CDCl_3$) δ ppm 1.39 (s, 9 H), 2.84-2.95 (m, 2 H), 3.06 (bs, 0.5 H), 3.69 (s, 3 H), 4.43-4.61 (m, 1 H), 4.72-4.80 (m, 0.5 H), 5.00 (s, 0.5 H), 5.12 (s, 0.5 H), 7.28-7.34 (m, 3 H), 7.37 (t, 1 H, J = 7.58 Hz), 7.42-7.47 (m, 1 H), 7.48-7.53 (m, 1 H), 7.55 (t, 1 H, J = 2.02 Hz). 19F-NMR (377 MHz, $CDCl_3$) δ ppm -204.18.

(R)-3-tert-butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-2-fluoro-butyric acid methyl ester (60 mg, 0.142 mmol) is treated with 4M HCl in dioxane (1.5mL). After being stirred at room temperature for 1h, the reaction mixture is concnetrated. The residue is used for a next step without further purification. HPLC retention time = 0.88 minutes (condition B): MS (m+1) = 322.

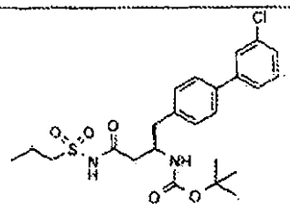
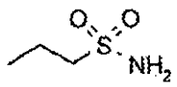
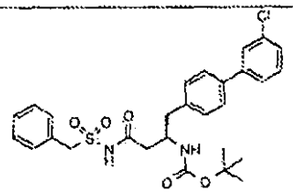
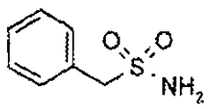
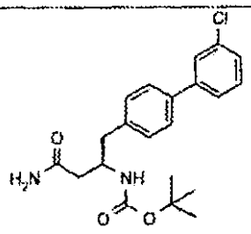
Intermediate 53-1: [(R)-1-(3'-chloro-biphenyl-4-ylmethyl)-3-methanesulfonylamino-3-oxo-propyl]-carbamic acid tert-butyl ester



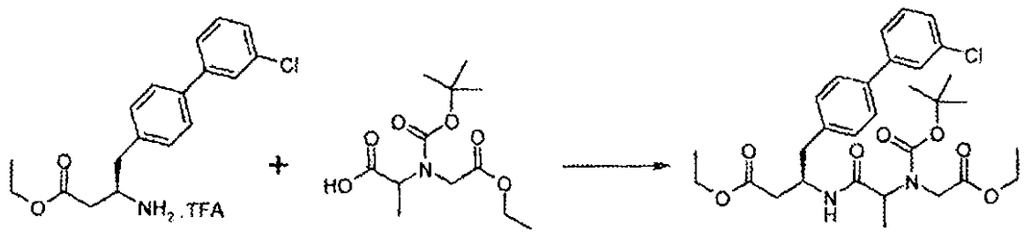
(R)-3-tert-butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-butyric acid ethyl ester (250 mg, 0.598 mmol) is treated with 2M NaOH aqueous solution (1 mL) in THF (1 mL) and EtOH (2 mL). After being stirred for 1h, the reaction miture is acidified with 1M HCl and extracted with EtOAc. The organic layer is washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. To a solution of this residue in DMF (2 mL) are added methylsulfonamide (85 mg, 0.897 mmol), EDC (172 mg, 0.897 mmol), HOAt (98 mg, 0.718 mmol), and Et_3N (0.125 mL, 0.897 mmol). After being stirred at room temperature overnight, the reaction mixture is diluted with EtOAc, washed with 1M HCl and brine. The organic layer is dried over Na_2SO_4 and cocentrated. The residue is purified by flash column chromatograpy (silica gel, eluent:

DCM/10%MeOH in DCM = 100:0 to 0:100) to give [(R)-1-(3'-chloro-biphenyl-4-ylmethyl)-3-methanesulfonylamino-3-oxo-propyl]-carbamic acid tert-butyl ester (244 mg). HPLC retentions time = 1.30 minutes (condition B); MS (m+1) = 467; 1H NMR (400 Mz, DMSO-d6) δ ppm 1.30 (s, 9 H), 2.41-2.48 (m, 2 H), 2.70-2.78 (m, 2 H), 3.18 (s, 3 H), 3.99-4.11 (m, 1 H), 7.28 (d, 2 H, *J* = 8.34 Hz), 7.38-7.44 (m, 1 H), 7.48 (t, 1 H, *J* =7.83 Hz), 7.59-7.66 (m, 3 H), 7.69 (s, 1 H).

Following compounds are prepared using similar procedure as described in example 53-1:

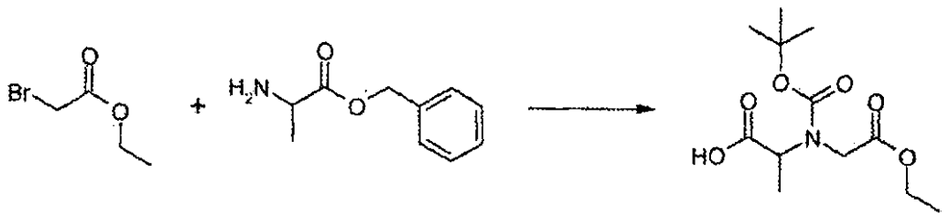
Example	Product	Reagent	HPLC-RT (condition)	MS (M+1)
Example 53-2			1.22 min. (condition B)	496
Example 53-3			1.33 min. (condition B)	544
Example 53-4		NH_4Cl	1.17 min. (condition B)	389

Intermediate 54-1: (R)-3-[2-(tert-butoxycarbonyl-ethoxycarbonylmethyl-amino)-propionylamino]-4-(3'-chloro-biphenyl-4-yl)-butyric acid ethyl ester



To a suspension of 2-(tert-butoxycarbonyl-ethoxycarbonylmethyl-amino)-propionic acid TFA salt (197 mg, 0.714 mmol) in THF (10 ml) at room temperature is added EDCI (219 mg, 1.142 mmol) and HOBT (164 mg, 1.071 mmol). The mixture is stirred at room temperature for 10 mins and then was added a solution of (R)-3-amino-4-(3'-chloro-biphenyl-4-yl)-butyric acid ethyl ester (202 mg, 0.571 mmol) in THF and TEA (0.199 ml, 1.428 mmol). The mixture is stirred at room temperature. Reverse phase HPLC [30 to 90% ACN-H_2O (0.1%TFA) over 10 min by X-Bridge phenyl column] give the title compound (290 mg, 71% yield). LCMS (condition B): 575 (M+1); retention time = 1.52 min.

Intermediate 54-2: 2-(tert-Butoxycarbonyl-ethoxycarbonylmethyl-amino)-propionic acid

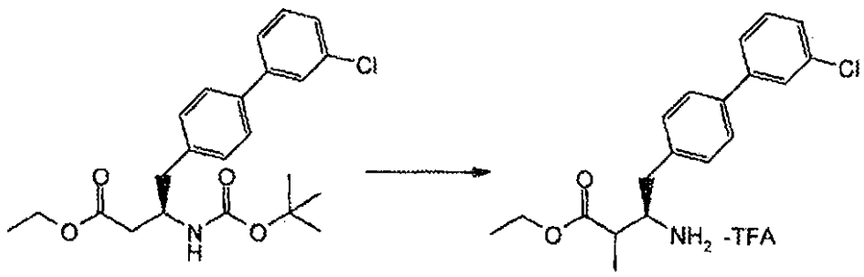


To a solution of H-DL-Ala-OBzl.p-tosylate (2.88 g, 8.20 mmol) in THF (80 ml) at room temperature was added TEA (3.43 ml, 24.60 mmol) and followed by ethyl bromoacetate (1.096 ml, 9.84 mmol). The reaction was stirred at room temperature over night. There were some white solid in the reaction. The reaction mixture was filtered off the white solid and concentrated for purification. Flash chromatography (silica gel, 2 to 4% EtOH/DCM) gave the title compound as an oil (1.7 g, 78% yield). LCMS (condition B): 266 (M+1); retention time = 0.70 min.

Next, to a solution of 2-(ethoxycarbonylmethyl-amino)-propionic acid benzyl ester (1.7 g, 6.41 mmol) in DCM (80 ml) at 0 °C was added BOC-anhydride (2.232 ml, 9.61 mmol) and followed by TEA (2.68 ml, 19.22 mmol). The reaction mixture was slowly warmed up to room temperature and stirred over night. The reaction was quenched by brine and was extracted with DCM. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate, filtered and concentrated to give the crude. Flash chromatography (silica gel, 5 to 10% acetone/heptane) gave the title compound as an oil (1.66 g, 71% yield). LCMS (condition B): 366 (M+1); retention time = 1.13 min.

Next, a solution of 2-(tert-butoxycarbonyl-ethoxycarbonylmethyl-amino)-propionic acid benzyl ester in EtOAc was hydrogenated under H_2 baloon by catalyst 10% Pd/C wet for 1 hr. The reaction was filtered off the catalyst and concentrated to give the crude for the next reaction.

Intermediate 55: (R)-3-Amino-4-(3'-chloro-biphenyl-4-yl)-2-methyl-butyric acid ethyl ester trifluoroacetate



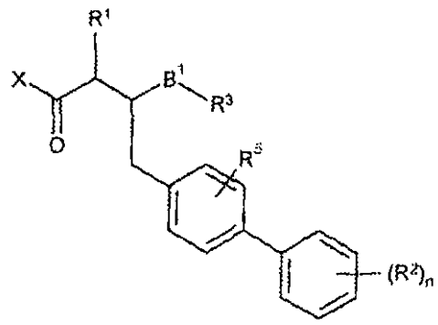
To a solution of (R)-3-tert-butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-butyric acid ethyl ester (300 mg, 0.718 mmol) in THF (10 ml) at -78 °C is added LiHMDS/THF (1M) (1.579 ml, 1.579 mmol). The reaction mixture is stirred at -78 °C for 50 min and then to this mixture is added methyl iodine (0.054 ml, 0.861 mmol) and the reaction is slowly warmed up to room temperature and stirred over night. The reaction is quenched by sat. NH_4Cl and is extracted with EtOAc. The combined organic layer is washed with brine and dried over anhydrous sodium sulfate, filtered and concentrated to give the crude. Reverse phase HPLC [20 to 90% ACN-H_2O (0.1%TFA) over 10 min by Sunfire C18] give (R)-3-tert-butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-2-methyl-butyric acid ethyl ester. LCMS (condition B): 432 (M+1); retention time = 1.55 min. To a solution of (R)-3-tert-butoxycarbonylamino-4-(3'-chloro-biphenyl-4-yl)-2-methyl-butyric acid ethyl ester (240 mg, 0.556 mmol) in DCM (2 ml) at room temperature was added TFA (1.070 ml, 13.89 mmol) and the mixture is stirred at room temperature. 1hr the reaction is done so the mixture is concentrated to give (R)-3-amino-4-(3'-chloro-biphenyl-4-yl)-2-methyl-butyric acid ethyl ester trifluoroacetate. LCMS (condition B): 332 (M+1); retention time = 1.00 min.

It can be seen that the compounds of the invention are useful as inhibitors of Neutral endopeptidase (EC 3.4.24.11) activity and therefore useful in the treatment of diseases and conditions associated with Neutral endopeptidase (EC 3.4.24.11) activity such as the diseases disclosed herein.

It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention.

CLAIMS

1. A compound of Formula I':



Formula I'

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, -SH, -S-C_{1-7}alkyl or NR^aR^b;

R^2 for each occurence, is independently C_{1-7}alkyl, halo, NO_2, CN, C_{1-7}alkanoylamino, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, -NR^aR^b, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^a and R^b for each occurrence are independently H or C_{1-7}alkyl;

R^3 is A^1-C(O)X^1 or A^2-R^4;

R^4 is C_{6-10}aryl or a heteroaryl, which can be monocyclic or bicyclic, and which can be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, hydroxyC_{1-7}alkyl, nitro, -NR^aR^b, -C(O)C_{1-7}alkyl, C(O)-O-C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{2-7}alkenyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl; or R^4 is a heterocyclyl which can be optionally substituted with one or more substituents independently selected from the group consisting of oxo, hydroxy, hydroxyC_{1-7}alkyl, amino, C(O)-O- C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl;

R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and

X and X^1 are independently OH, -O-C_{1-7}alkyl, -NR^aR^b, -$NHS(O)_2$-C_{1-7}alkyl, -$NHS(O)_2$-benzyl or -O- C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_{6-10}aryl, heteroaryl, heterocyclyl, $C(O)NH_2$, C(O)NH- C_{1-6}alkyl, and C(O)N(C_{1-6}alkyl)$_2$;

B^1 is –C(O)NH- or –NHC(O)-;

A^1 is a bond or a linear or branched C_{1-7}alkylene ; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{3-7}cycloalkyl,

C_{1-7}alkoxy, hydroxy and O-acetate; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

A^1 is a linear or branched C_{1-7}alkenylene; or

A^1 is a linear C_{1-4} alkylene wherein one or more carbon atom(s) is/are replaced with an heteroatom selected from O, NR^c; and A^1 is optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{1-7}alkyl; in which R^c for each occurrence, is independently H, C_{1-7}alkyl, -C(O)-O-C_{1-7}alkyl or $-CH_2C(O)OH$; or

A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, $-NR^aR^b$, $-OCH_2CO_2H$, and $-OCH_2C(O)NH_2$; or

A^1 is a C_{3-7}cycloalkyl;

A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein A^1 may be in either direction; and

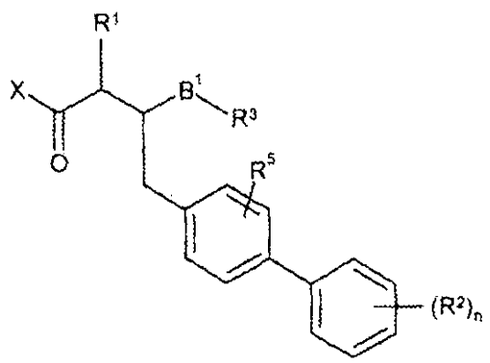
A^2 is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

n is 0, 1, 2, 3, 4 or 5;

wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

2. A compound according to claim 1 of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or C_{1-7}alkyl;

R^2 for each occurence, is independently C_{1-7}alkyl, halo, NO_2, CN, C_{1-7}alkanoylamino, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, -NR^aR^b, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^a and R^b for each occurrence are independently H or C_{1-7}alkyl;

R^3 is A^1-$C(O)X^1$ or A^2-R^4;

R^4 is C_{6-10}aryl or a heteroaryl, which can be monocyclic or bicyclic, and which can be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, hydroxyC_{1-7}alkyl, amino, C(O)-O- C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl; or R^4 is a heterocyclyl which can be optionally substituted with one or more substituents independently selected from the group consisting of oxo, hydroxy, hydroxyC_{1-7}alkyl, amino, C(O)-O- C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl;

R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and

X and X^1 are independently OH, -O-C_{1-7}alkyl, NR^aR^b, or -O- C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_{6-10}aryl, heteroaryl, heterocyclyl, $C(O)NH_2$, C(O)NH- C_{1-6}alkyl, and $C(O)N(C_{1-6}alkyl)_2$;

B^1 is –C(O)NH- or –NHC(O)-;

A^1 is a bond or a linear or branched C_{1-7}alkylene ; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{3-7}cycloalkyl, C_{1-7}alkoxy, hydroxy and O-acetate; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, -NR^aR^b, -OCH_2CO_2H, and -$OCH_2C(O)NH_2$; or

A^1 is a C_{3-7}cycloalkyl;

A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein A^1 may be in either direction; and

A^2 is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

n is 0, 1, 2, 3, 4 or 5;

wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

3. The compound of Claim 1 or 2 wherein:

R^1 is H or C_{1-7}alkyl;

R^2 for each occurrence, is independently C_{1-7}alkyl, halo, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, -NR^aR^b, C_{6-20}aryl, heteroaryl or heterocyclyl; wherein R^a and R^b for each occurrence are independently H or C_{1-7}alkyl;

R^3 is A^1-$C(O)X^1$ or A^2-R^4;

R^4 is C_{6-20}aryl or a heteroaryl, each of which can be monocyclic or bicyclic and each of which can be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl;

R^5 is H; and

X and X^1 are independently OH, -O-C_{1-7}alkyl or NR^aR^b;

B^1 is –C(O)NH- or –NHC(O)-;

A^1 is a linear or branched C_{1-7}alkylene ; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{3-7}cycloalkyl, C_{1-7}alkoxy, hydroxy and O-acetate; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, -NR^aR^b, -OCH_2CO_2H, and -$OCH_2C(O)NH_2$; and

A^2 is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl; and

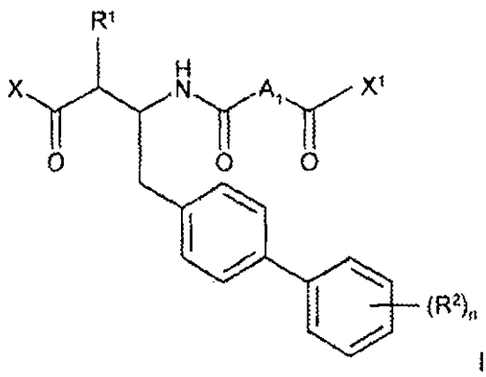
n is 0, 1, 2, 3, 4 or 5;

wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

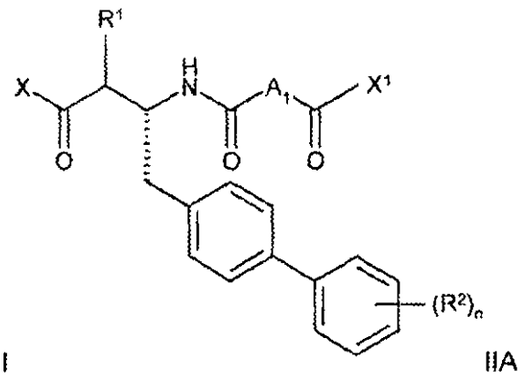
each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein

each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S, or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1, 2 or 3 having Formula II or IIA:



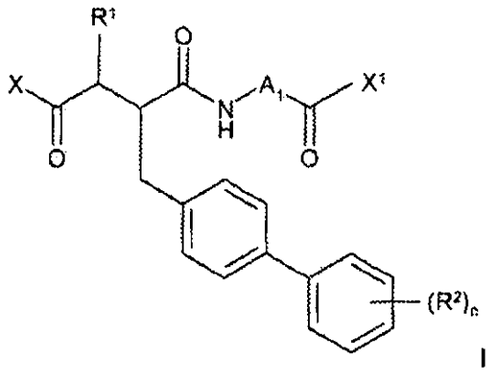
II



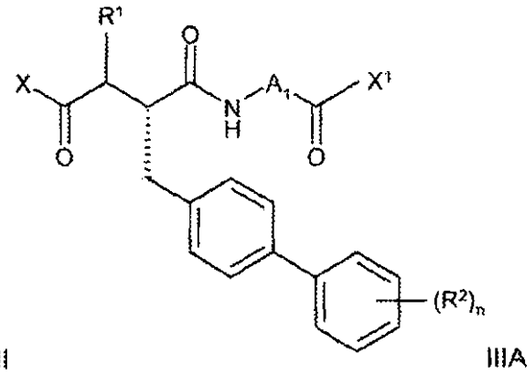
IIA

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, 2 or 3 having formula III or IIIA:



III



IIIA

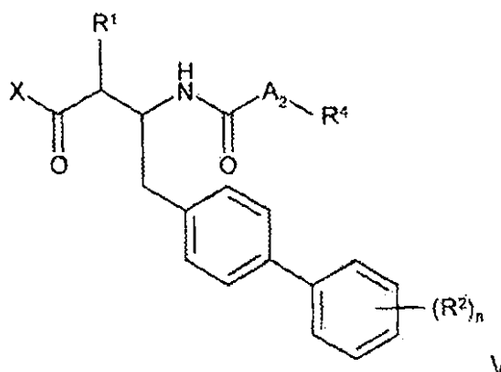
or a pharmaceutically acceptable salt thereof.

6. The compound of any of claims 1 to 5 wherein $\mathbf{A^1}$ is an optionally substituted linear or branched C_{1-7} alkylene, or a pharmaceutically acceptable salt thereof.

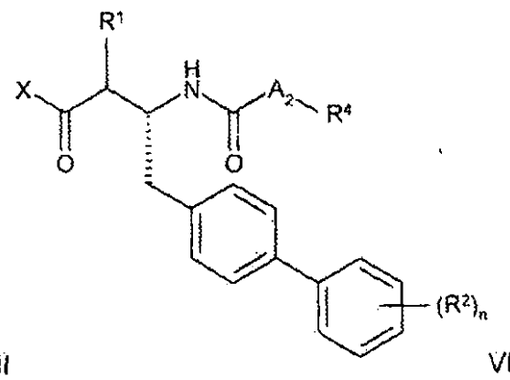
7. The compounds of any of claims 1 to 6 wherein $\mathbf{A^1}$ is CH_2CH_2, or a pharmaceutically acceptable salt thereof.

8. The compound of any of claims 1 to 5 wherein A^1 is an optionally substituted phenyl or heteroaryl, or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1, 2 or 3 having Formula VII or VIIA:



VII



VIIA

or a pharmaceutically acceptable salt thereof.

10. The compound of claim 9 wherein A^2 is a bond or CH_2 or CH_2-CH_2, or a pharmaceutically acceptable salt thereof.

11. The compound of any of claims 1 to 10 wherein R^1 is H, R^2 is independently halo, C_{1-7}alkoxy, hydroxy, C_{1-7}alkyl or halo-C_{1-7}alkyl , n is 0, 1 or 2 and X and X^1 are independently OH or -O-C_{1-7}alkyl, or a pharmaceutically acceptable salt thereof.

12 The compounds of any of claims 1 to 11 wherein n is 1 or 2; R^2 is meta-chloro or meta-fluoro and the other optional R^2 group is halo, C_{1-7}alkyl, halo-C_{1-7}alkyl, hydroxy and C_{1-7}alkoxy, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

14. A combination comprising: a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and one or more therapeutically active agents selected from HMG-Co-A reductase inhibitor, an anigiotensin receptor blocker, angiotensin converting enzyme inhibitor, a calcium channel blocker, an endothelin antagonist, a renin

inhibitor, a diuretic, an ApoA-I mimic, an anti-diabetic agent, an obesity-reducing agent, an aldosterone receptor blocker, an endothelin receptor blocker, an aldosterone synthase inhibitors, a CETP inhibitor and a phosphodiesterase of type 5 (PDE5) inhibitor.

15. A method of inhibiting neutral endopeptidase EC. 3.4. 24.11. activity in a subject in need thereof, comprising: administering to the subject a therapeutically effective amount of the compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof.

16. The method according to claim 15, wherein the disorder or the disease is selected from hypertension, pulmonary hypertension, isolated systolic hypertension, resistant hypertension, peripheral vascular disease, heart failure, congestive heart failure, left ventricular hypertrophy, angina, renal insufficiency, renal failure, diabetic nephropathy, non-diabetic nephropathy, nephroic syndrome, glomerulonephritis, scleroderma, glomerular sclerosis, proteinurea of primary renal disease, renal vascular hypertention, diabetic retinopathy and end-stage renal disease (ESRD), endothelial dysfunction, diastolic dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation (AF), cardiac fibrosis,atrial flutter, detrimental vascular remodeling, plaque stabilization, myocardial infarction (MI), renal fibrosis, polycystic kidney disease (PKD), pulmonary arterial hypertension, renal failure, cyclical oedema, Menières disease, hyperaldosteroneism hypercalciuria, ascites, glaucoma, menstrual disorders, preterm labour, pre-eclampsia, endometriosis, and reproductive disorders, asthma, obstructive sleep apnea, inflammation, leukemia, pain, epilepsy, affective disorders, depression, psychotic condition, dementia, geriatric confusion, obesity and gastrointestinal disorders, wound healing, septic shock, gastric acid secretion dysfunction, hyperreninaemia, cystic fibrosis, restenosis, type-2 diabetes, metabolic syndrome, diabetic complications, atherosclerosis, male and female sexual dysfunction.

17. The compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use as a medicament.

18. Use of the compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for the treatment of a disorder or disease associated with neutral endopeptidase EC. 3.4. 24.11. activity in a subject in need of such treatment.

19. The use of claim 18, wherein the disorder or disease is selected from hypertension, pulmonary hypertension, isolated systolic hypertension, resistant hypertension, peripheral vascular disease, heart failure, congestive heart failure, left ventricular hypertrophy, angina, renal insufficiency, renal failure, diabetic nephropathy, non-diabetic nephropathy, nephroic syndrome, glomerulonephritis, scleroderma, glomerular sclerosis, proteinurea of primary renal disease, renal vascular hypertention, diabetic retinopathy and end-stage renal disease (ESRD), endothelial dysfunction, diastolic dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation (AF), cardiac fibrosis, atrial flutter, detrimental vascular remodeling, plaque stabilization, myocardial infarction (MI), renal fibrosis, polycystic kidney disease (PKD), pulmonary arterial hypertension, renal failure, cyclical oedema, Menières disease, hyperaldosteroneism hypercalciuria, ascites, glaucoma, menstrual disorders, preterm labour, pre-eclampsia, endometriosis, and reproductive disorders, asthma, obstructive sleep apnea, inflammation, leukemia, pain, epilepsy, affective disorders, depression, psychotic condition, dementia, geriatric confusion, obesity and gastrointestinal disorders, wound healing, septic shock, gastric acid secretion dysfunction, hyperreninaemia, cystic fibrosis, restenosis, type-2 diabetes, metabolic syndrome, diabetic complications, atherosclerosis, male and female sexual dysfunction.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/057247

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/82 C07D239/36 C07D261/18 C07D271/06 C07C233/47
A61K31/21 A61K31/435
ADD.
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 C07C A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 199227 Thomson Scientific, London, GB; AN 1992-223453 XP002591646 & JP 4 149166 A (NIPPON KAYAKU KK) 22 May 1992 (1992-05-22)	1-4,11, 13-19
A	* abstract compound with RN:144139-09-3	5-10,12
A	GB 2 037 754 A (NIPPON KAYAKU KK) 16 July 1980 (1980-07-16) line 1 - page 15, line 10	1-19
A	EP 0 497 192 A2 (HOFFMANN LA ROCHE [CH]) 5 August 1992 (1992-08-05) page 46; claims 1,8	1-19

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[X] Further documents are listed in the continuation of Box C.

[X] 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
13 July 2010	23/07/2010

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/057247

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	W. YAO ET AL: "Potent P1' biphenylmethyl substituted aggrecanase inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 12, 2002, pages 101-104, XP002591647 Pergamon, Elsevier Science ISSN: 0960-894X table 1	1-19

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 5304549 A	19-04-1994

SOLICITUD INTERNACIONAL PUBLICADA DE ACUERDO CON EL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (TCP)

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(43) **Fecha de Publicación Internacional**
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(10) **Número de Publicación Internacional**
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C07D 239/36 (2006.01) *A61K 31/21* (2006.01)
C07D 261/18 (2006.01) *A61K 31/435* (2006.01)
C07D 271/06 (2006.01)

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(22) **Fecha de Presentación Internacional:**
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(25) **Idioma de Presentación:** Inglés

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(30) **Información de Prioridad**

61/181,756	28-Mayo-2009 (28.05.2009)	US
61/263,145	20-Noviembre-2009 (23.04.2010)	US
61/324,943	16-Abril-2010 (16.04.2010)	US

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(74) **Agente : VOEGELI-LANGE, Regina**; Novartis Pharma AG, Departamento de Patentes, CH-4002 Basilea (CH).

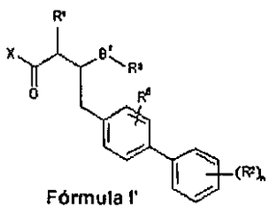
(81) **Estados (Países) Designados** (*a menos que se indique de otra manera, para cada tipo de protección nacional disponible*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU,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

(84) **Estados (Países) Designados** (*a menos que se indique de otra manera, para cada tipo de protección regional disponible*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasiáticos (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europeos (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaraciones de acuerdo con la Regla 4.17:
-- *con respecto al derecho de la solicitante de solicitar y otorgársele una patente (Regla 4.17(ii))*

Publicada:
-- *con reporte de búsqueda internacional (Art. 21(3))*

(54) Título : DERIVADOS AMINO-PROPIÓNICOS SUSTITUIDOS COMO INHIBIDORES DE NEPRILISINA



Fórmula I'

(57) Resumen:

La presente invención proporciona un compuesto de la fórmula I', o una sal farmacéuticamente aceptable del mismo, en donde R^1, R^2, R^3, R^5, B^1, X y n se definen en la presente. La invención también se refiere a un método para la elaboración de los compuestos de la invención, y a sus usos terapéuticos. La presente invención proporciona además una combinación de agentes farmacológicamente activos y una composición farmacéutica.

DERIVADOS AMINO-PROPIÓNICOS SUSTITUIDOS COMO INHIBIDORES DE NEPRILISINA

ANTECEDENTES DE LA INVENCIÓN

Los péptidos natriuréticos auriculares (ANP) endógenos, también denominados como factores natriuréticos auriculares (ANF) tienen funciones diuréticas, natriuréticas y vaso-relajantes en los mamíferos. Los factores natriuréticos auriculares (ANF) naturales se inactivan metabólicamente, en particular mediante una enzima degradante que se ha reconocido que corresponde a la enzima de endopeptidasa neutra (NEP) EC 3.4.24.11, también responsable, por ejemplo, de la inactivación metabólica de las encefalinas.

La endopeptidasa neutra (EC 3.4.24.11; encefalinasa; auriculopeptidasa; NEP) es una metaloproteasa que contiene zinc que disocia una variedad de sustratos peptídicos sobre el lado de amino de los residuos hidrofóbicos [véase *Pharmacol Rev*, Volumen 45, página 87 (1993)]. Los sustratos para esta enzima incluyen, pero no se limitan a, péptido natriurético auricular (ANP, también conocido como ANF), péptido natriurético del cerebro (BNP), met- y leu-encefalina, bradiquinina, neuroquinina A, endotelina-1 y sustancia P. El péptido natriurético auricular (ANP) es un potente agente vaso-relajante y natriurético [véase *J Hypertens*, Volumen 19, página 1923 (2001)]. La infusión del péptido natriurético auricular (ANP) en los sujetos normales daba como resultado una notoria mejora reproducible de la natriuresis y diuresis, incluyendo aumentos en la

excreción fraccionaria de sodio, en la velocidad del flujo urinario, y en el índice de filtración glomerular [véase *J Clin Pharmacol*, Volumen 27, página 927 (1987)]. Sin embargo, el péptido natriurético auricular (ANP) tiene una corta vida media en la circulación, y se ha demostrado que la endopeptidasa neutra (NEP) en las membranas de la corteza renal es la principal enzima responsable de la degradación de este péptido [véase *Peptides*, Volumen 9, página 173 (1988)]. Por consiguiente, los inhibidores de NEP (inhibidores de endopeptidasa neutra, NEPi) deben aumentar los niveles en plasma del péptido natriurético auricular (ANP) y, por consiguiente, se espera que induzcan los efectos natriuréticos y diuréticos.

Esta enzima está involucrada en la descomposición de varios oligopéptidos bioactivos, disociando los enlaces peptídicos sobre el lado de amino de los residuos de aminoácidos hidrofóbicos. Los péptidos metabolizados incluyen los péptidos natriuréticos auriculares (ANP), bombesina, bradiquinina, péptido relacionado con el gen de calcitonina, endotelinas, encefalinas, neurotensina, sustancia P, y péptido intestinal vasoactivo. Algunos de estos péptidos tienen potentes funciones vasodilatadoras y de neuro-hormonas, actividad diurética y natriurética, o median los efectos del comportamiento.

BREVE DESCRIPCIÓN DE LA INVENCIÓN:

El objetivo de la presente invención es proporcionar compuestos novedosos que son útiles como inhibidores de la endopeptidasa neutra, por ejemplo, como inhibidores de la enzima

degradante del factor natriurético auricular (ANF) en los mamíferos, para prolongar y potenciar las propiedades diuréticas, natriuréticas y vasodilatadoras del factor natriurético auricular (ANF) en los mamíferos, mediante la inhibición de la degradación de los mismos hasta metabolitos menos activos.

Los compuestos de esta invención, por consiguiente, son particularmente útiles para el tratamiento de las condiciones y los trastornos que respondan a la inhibición de la endopeptidasa neutra (NEP) EC 3.4.24.11.

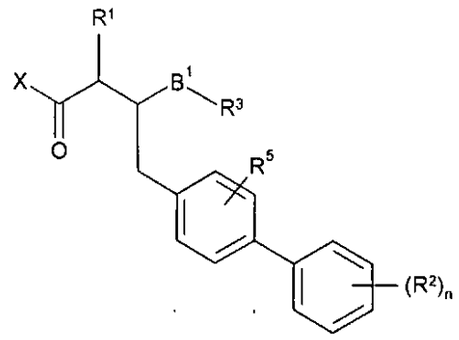
Por consiguiente, los compuestos de la invención, mediante la inhibición de la endopeptidasa neutra EC.3.4.24.11, pueden potenciar los efectos biológicos de los péptidos bioactivos. Por consiguiente, en particular los compuestos tienen utilidad en el tratamiento de un número de trastornos, incluyendo hipertensión, hipertensión pulmonar, hipertensión sistólica aislada, hipertensión resistente, enfermedad vascular periférica, insuficiencia cardíaca, insuficiencia cardíaca congestiva, hipertrofia de ventrículo izquierdo, angina, insuficiencia renal (diabética o no diabética), falla renal (incluyendo edema y retención de sal), nefropatía diabética, nefropatía no diabética, síndrome nefrótico, glomerulonefritis, esclerodermia, esclerosis glomerular, proteinuria de enfermedad renal primaria, hipertensión vascular renal, retinopatía diabética y enfermedad renal en etapa final (ESRD), disfunción endotelial, disfunción diastólica, cardiomiopatía hipertrófica, miopatía cardíaca diabética, arritmias supraventriculares y ventriculares, fibrilación

auricular (AF), fibrosis cardíaca, flúter auricular, remodelación vascular perjudicial, estabilización de placa, infarto de miocardio (MI), fibrosis renal, enfermedad de riñón poliquístico (PKD), hipertensión arterial pulmonar, falla renal (incluyendo edema y retención de sal), edema cíclico, enfermedad de Menières, hiperaldosteronismo (primario y secundario) e hipercalciuria, ascitas. En adición, debido a su capacidad para potenciar los efectos del factor natriurético auricular, los compuestos tienen utilidad en el tratamiento de glaucoma. Como un resultado adicional de su capacidad para inhibir la endopeptidasa neutra E.C.3.4.24.11, los compuestos de la invención pueden tener actividad en otras áreas terapéuticas, incluyendo, por ejemplo, el tratamiento de trastornos menstruales, parto a pretérmino, pre-eclampsia, endometriosis, y trastornos reproductivos (en especial infertilidad masculina y femenina, síndrome de ovario poliquístico, fracaso de implante). También, los compuestos de la invención deben tratar asma, apnea obstructiva del sueño, inflamación, leucemia, dolor, epilepsia, trastornos afectivos, tales como depresión y condición psicótica, tal como demencia y confusión geriátrica, obesidad y trastornos gastrointestinales (en especial diarrea y síndrome de intestino irritable), sanado de heridas (en especial úlceras diabéticas y venosas, y llagas por decúbito), choque séptico, modulación de secreción de ácido gástrico, tratamiento de hiperreninemia, fibrosis quística, restenosis, diabetes tipo 2, síndrome metabólico, complicaciones diabéticas y ateroesclerosis, disfunción sexual

masculina y femenina. En una modalidad preferida, los compuestos de la invención son útiles en el tratamiento de trastornos cardiovasculares.

La invención pertenece a compuestos, a métodos para utilizarlos, y al uso de los mismos como se describe en la presente. Los ejemplos de los compuestos de la invención incluyen los compuestos de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable de los mismos, y los compuestos de los Ejemplos .

La invención, por consiguiente, proporciona un compuesto de la fórmula (I'):



Fórmula I'

o una sal farmacéuticamente aceptable del mismo, en donde:

R^1 es H, alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, -SH, -S-alquilo de 1 a 7 átomos de carbono o NR^aR^b;

R^2 por cada presentación, es independientemente alquilo de 1 a 7 átomos de carbono, halógeno, NO_2, CN, alcanoílo de 1 a 7 átomos de carbono-amino, cicloalquilo de 3 a 7 átomos de carbono,

hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, $-NR^aR^b$, arilo de 6 a 10 átomos de carbono, heteroarilo o heterociclilo; en donde R^a y R^b por cada presentación, son independientemente H o alquilo de 1 a 7 átomos de carbono;

R^3 es A^1-$C(O)X^1$ o A^2-R^4;

R^4 es arilo de 6 a 10 átomos de carbono, o un heteroarilo, el cual puede ser monocíclico o bicíclico, y el cual puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en hidroxilo, hidroxi-alquilo de 1 a 7 átomos de carbono, nitro, $-NR^aR^b$, -C(O)-alquilo de 1 a 7 átomos de carbono, C(O)-O-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, alquenilo de 2 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, heteroarilo, $-NHSO_2$-alquilo de 1 a 7 átomos de carbono y bencilo; o R^4 es un heterociclilo, el cual puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en oxo, hidroxilo, hidroxi-alquilo de 1 a 7 átomos de carbono, amino, C(O)-O-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, heteroarilo, $-NHSO_2$-alquilo de 1 a 7 átomos de carbono y bencilo;

R^5 es H, halógeno, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, o halo-

alquilo de 1 a 7 átomos de carbono; y

X y X^1 son independientemente OH, -O-alquilo de 1 a 7 átomos de carbono, -NR^aR^b, -$NHS(O)_2$-alquilo de 1 a 7 átomos de carbono, -$NHS(O)_2$-bencilo u -O-arilo de 6 a 10 átomos de carbono; en donde el alquilo está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en arilo de 6 a 10 átomos de carbono, heteroarilo, heterociclilo, $C(O)NH_2$, C(O)NH-alquilo de 1 a 6 átomos de carbono, y C(O)N(alquilo de 1 a 6 átomos de carbono)$_2$;

B^1 es –C(O)NH- o –NHC(O)-;

A^1 es un enlace o un alquileno de 1 a 7 átomos de carbono lineal o ramificado; que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno, cicloalquilo de 3 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, y O-acetato; en donde dos grupos alquilo geminales pueden combinarse opcionalmente para formar un cicloalquilo de 3 a 7 átomos de carbono; o

A^1 es un alquenileno de 1 a 7 átomos de carbono lineal o ramificado; o

A^1 es un alquileno lineal de 1 a 4 átomos de carbono, en donde uno o más átomos de carbono son reemplazados con un heteroátomo seleccionado a partir de O, NR^c; y A^1 está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno y alquilo de 1 a 7 átomos

de carbono; en donde R^c por cada presentación, es independientemente H, alquilo de 1 a 7 átomos de carbono, -C(O)-O-alquilo de 1 a 7 átomos de carbono, o $-CH_2C(O)OH$; o

A^1 es un fenilo o un heteroarilo; cada uno de los cuales está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, $-NR^aR^b$, $-OCH_2CO_2H$, y $-OCH_2C(O)NH_2$; o

A^1 es un cicloalquilo de 3 a 7 átomos de carbono;

A^1 es -alquileno de 1 a 4 átomos de carbono-arilo de 6 a 10 átomos de carbono-, -alquileno de 1 a 4 átomos de carbono-heteroaril- o -alquileno de 1 a 4 átomos de carbono-heterociclil-, en donde A^1 puede estar en cualquier dirección; y

A^2 es un enlace o un alquileno de 1 a 7 átomos de carbono lineal o ramificado, que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, O-acetato y cicloalquilo de 3 a 7 átomos de carbono;

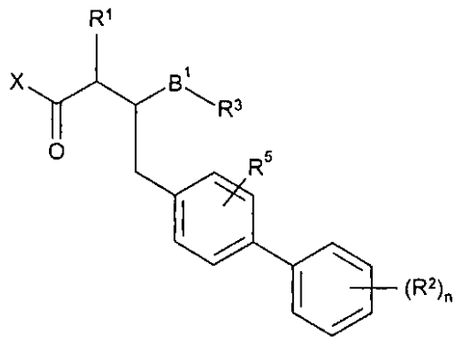
n es 0, 1, 2, 3, 4 ó 5;

en donde cada heteroarilo es un anillo aromático monocíclico o bicíclico que comprende de 5 a 10 átomos del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, y

cada heterociclilo es una fracción monocíclica saturada o

parcialmente saturada, pero no aromática, la cual comprende de 4 a 7 átomos del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, en donde cada heteroátomo de un heteroarilo o de un heterociclilo se selecciona independientemente a partir de O, N y S.

La invención, por consiguiente, proporciona un compuesto de la fórmula (I):



Fórmula I

o una sal farmacéuticamente aceptable del mismo, en donde:

R^1 es H o alquilo de 1 a 7 átomos de carbono;

R^2 por cada presentación, es independientemente alquilo de 1 a 7 átomos de carbono, halógeno, NO_2, CN, alcanoílo de 1 a 7 átomos de carbono-amino, cicloalquilo de 3 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, $-NR^aR^b$, arilo de 6 a 10 átomos de carbono, heteroarilo o heterociclilo; en donde R^a y R^b por cada presentación, son independientemente H o alquilo de 1 a 7 átomos de carbono;

R^3 es A^1-C(O)X^1 o A^2-R^4;

R^4 es arilo de 6 a 10 átomos de carbono, o un heteroarilo, el

cual puede ser monocíclico o bicíclico, y el cual puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en hidroxilo, hidroxi-alquilo de 1 a 7 átomos de carbono, amino, C(O)-O-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, heteroarilo, -$NHSO_2$-alquilo de 1 a 7 átomos de carbono y bencilo; o R^4 es un heterociclilo, el cual puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en oxo, hidroxilo, hidroxi-alquilo de 1 a 7 átomos de carbono, amino, C(O)-O-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, heteroarilo, -$NHSO_2$-alquilo de 1 a 7 átomos de carbono y bencilo;

R^5 es H, halógeno, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, o halo-alquilo de 1 a 7 átomos de carbono; y

X y X^1 son independientemente OH, -O-alquilo de 1 a 7 átomos de carbono, NR^aR^b, u -O-arilo de 6 a 10 átomos de carbono; en donde el alquilo está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en arilo de 6 a 10 átomos de carbono, heteroarilo, heterociclilo, $C(O)NH_2$, C(O)NH-alquilo de 1 a 6 átomos de carbono,

y C(O)N(alquilo de 1 a 6 átomos de carbono)$_2$;

B^1 es –C(O)NH- o –NHC(O)-;

A^1 es un enlace o un alquileno de 1 a 7 átomos de carbono lineal o ramificado, que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno, cicloalquilo de 3 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, y O-acetato; en donde dos grupos alquilo geminales pueden combinarse opcionalmente para formar un cicloalquilo de 3 a 7 átomos de carbono; o

A^1 es un fenilo o un heteroarilo; cada uno de los cuales está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, $-NR^aR^b$, $-OCH_2CO_2H$, y $-OCH_2C(O)NH_2$; o

A^1 es un cicloalquilo de 3 a 7 átomos de carbono;

A^1 es -alquileno de 1 a 4 átomos de carbono-arilo de 6 a 10 átomos de carbono-, -alquileno de 1 a 4 átomos de carbono-heteroaril- o -alquileno de 1 a 4 átomos de carbono-heterociclil-, en donde A^1 puede estar en cualquier dirección; y

A^2 es un enlace o un alquileno de 1 a 7 átomos de carbono lineal o ramificado, que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo

que consiste en halógeno, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, O-acetato y cicloalquilo de 3 a 7 átomos de carbono;

n es 0, 1, 2, 3, 4 ó 5;

en donde cada heteroarilo es un anillo aromático monocíclico o bicíclico que comprende de 5 a 10 átomos del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, y

cada heterociclilo es una fracción monocíclica saturada o parcialmente saturada, pero no aromática, la cual comprende de 4 a 7 átomos del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, en donde cada heteroátomo de un heteroarilo o de un heterociclilo se selecciona independientemente a partir de O, N y S.

En otra modalidad, la invención pertenece a un método para el tratamiento de trastornos o enfermedades que respondan a la inhibición de la endopeptidasa neutra EC 3.4. 24.11 (NEP), en un sujeto, mediante la administración al sujeto, de una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, de tal manera que se trate el trastorno o la enfermedad que responda a la inhibición de la endopeptidasa neutra EC 3.4. 24.11 (NEP) en el sujeto.

En todavía otra modalidad, la invención pertenece a un método para el tratamiento de hipertensión, hipertensión pulmonar, hipertensión sistólica aislada, hipertensión resistente, enfermedad vascular periférica, insuficiencia cardíaca, insuficiencia cardíaca

congestiva, hipertrofia de ventrículo izquierdo, angina, insuficiencia renal (diabética o no diabética), falla renal (incluyendo edema y retención de sal), nefropatía diabética, nefropatía no diabética, síndrome nefrótico, glomerulonefritis, esclerodermia, esclerosis glomerular, proteinuria de enfermedad renal primaria, hipertensión vascular renal, retinopatía diabética y enfermedad renal en etapa final (ESRD), disfunción endotelial, disfunción diastólica, cardiomiopatía hipertrófica, miopatía cardíaca diabética, arritmias supraventriculares y ventriculares, fibrilación auricular (AF), fibrosis cardíaca, flúter auricular, remodelación vascular perjudicial, estabilización de placa, infarto de miocardio (MI), fibrosis renal, enfermedad de riñón poliquístico (PKD), hipertensión arterial pulmonar, falla renal (incluyendo edema y retención de sal), edema cíclico, enfermedad de Menières, hiperaldosteronismo (primario y secundario) e hipercalciuria, ascitas, glaucoma, trastornos menstruales, parto a pretérmino, pre-eclampsia, endometriosis, y trastornos reproductivos (en especial infertilidad masculina y femenina, síndrome de ovario poliquístico, fracaso de implante), asma, apnea obstructiva del sueño, inflamación, leucemia, dolor, epilepsia, trastornos afectivos, tales como depresión y condición psicótica, tal como demencia y confusión geriátrica, obesidad y trastornos gastrointestinales (en especial diarrea y síndrome de intestino irritable), sanado de heridas (en especial úlceras diabéticas y venosas, y llagas por decúbito), choque séptico, disfunción de secreción de ácido gástrico, hiperreninemia, fibrosis quística,

restenosis, diabetes tipo 2, síndrome metabólico, complicaciones diabéticas y ateroesclerosis, disfunción sexual masculina y femenina; el cual comprende administrar al sujeto una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, de tal manera que se trate al sujeto.

En todavía otra modalidad, la invención pertenece a composiciones farmacéuticas, las cuales comprenden un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, y uno o más vehículos farmacéuticamente aceptables.

En todavía otra modalidad, la invención pertenece a combinaciones que incluyen un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, y a combinaciones farmacéuticas de uno o más agentes terapéuticamente activos.

En otra modalidad, la invención pertenece a un método para inhibir la endopeptidasa neutra EC 3.4. 24.11 en un sujeto, mediante la administración al sujeto, de una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o de una sal farmacéuticamente aceptable del mismo, de tal manera que se inhiba la endopeptidasa neutra EC 3.4. 24.11.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN:

Compuestos de la Invención

Las referencias posteriormente en la presente a los

compuestos de la fórmula I o I' se aplican igualmente a los compuestos de acuerdo con cualquiera de las fórmulas IA a VIIC.

Las referencias posteriormente en la presente a las modalidades de la invención se aplican igualmente a los compuestos de la fórmula I o I' y a los compuestos de acuerdo con cualquiera de las fórmulas IA a VIIC, siempre que estén presentes las modalidades.

En la presente se describen diferentes modalidades de la invención. Se reconocerá que las características especificadas en cada modalidad se pueden combinar con otras características especificadas para proporcionar modalidades adicionales.

En una modalidad, la invención proporciona un compuesto de la fórmula I o I', o una sal farmacéuticamente aceptable del mismo, en donde:

R^1 es H o alquilo de 1 a 7 átomos de carbono;

R^2 por cada presentación, es independientemente alquilo de 1 a 7 átomos de carbono, halógeno, cicloalquilo de 3 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, $-NR^aR^b$, arilo de 6 a 10 átomos de carbono, heteroarilo o heterociclilo; en donde R^a y R^b por cada presentación, son independientemente H o alquilo de 1 a 7 átomos de carbono;

R^3 es A^1-$C(O)X^1$ o A^2-R^4;

R^4 es arilo de 6 a 10 átomos de carbono, o un heteroarilo, el cual puede ser monocíclico o bicíclico, y el cual puede estar

opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono arilo de 6 a 10 átomos de carbono, heteroarilo, -$NHSO_2$-alquilo de 1 a 7 átomos de carbono y bencilo;

R^5 es H; y

X y X^1 son independientemente OH, -O-alquilo de 1 a 7 átomos de carbono o NR^aR^b;

B^1 es –C(O)NH- o –NHC(O)-;

A^1 es un alquileno de 1 a 7 átomos de carbono lineal o ramificado, que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno, cicloalquilo de 3 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, y O-acetato; en donde dos grupos alquilo geminales pueden combinarse opcionalmente para formar un cicloalquilo de 3 a 7 átomos de carbono; o

A^1 es un fenilo o un heteroarilo; cada uno de los cuales está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, -NR^aR^b, -OCH_2CO_2H, y -$OCH_2C(O)NH_2$; y

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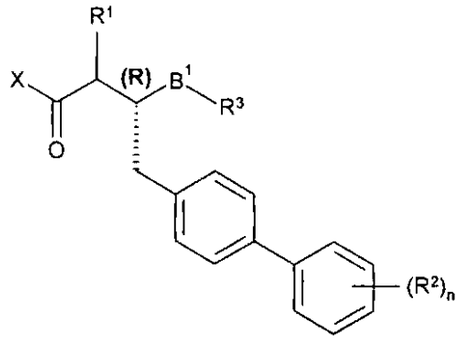
A^2 es un enlace o un alquileno de 1 a 7 átomos de carbono lineal o ramificado, que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, O-acetato y cicloalquilo de 3 a 7 átomos de carbono; y

n es 0, 1, 2, 3, 4 ó 5;

en donde cada heteroarilo es un anillo aromático monocíclico o bicíclico que comprende de 5 a 10 átomos del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, y

cada heterociclilo es una fracción monocíclica saturada o parcialmente saturada, pero no aromática, la cual comprende de 4 a 7 átomos del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, en donde cada heteroátomo de un heteroarilo o de un heterociclilo se selecciona independientemente a partir de O, N y S.

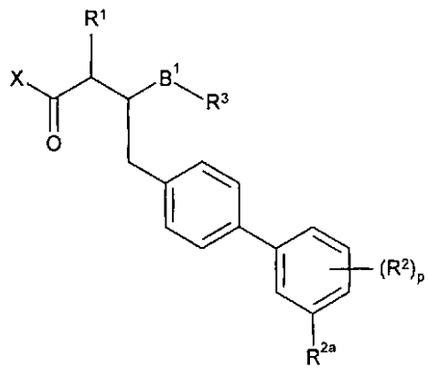
Ciertos compuestos de la fórmula I o I' incluyen los compuestos de la fórmula IA, en donde la estereoquímica en el átomo de carbono que lleva el grupo bifenilo es (R):



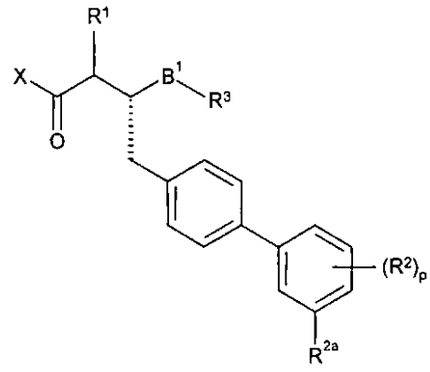
Fórmula IA.

o una sal farmacéuticamente aceptable de los mismos, en donde X, R^1, R^2, B^1, R^3 y n tienen las definiciones de la fórmula I o I' anteriores.

En una modalidad, la invención pertenece a los compuestos de la fórmula I o I', o a una sal farmacéuticamente aceptable de los mismos, en donde n es 1, 2, 3, 4 ó 5; R^2 es halógeno y está unido a la posición meta, y los otros grupos R^2 opcionales son independientemente alquilo de 1 a 7 átomos de carbono, NO_2, CN, halógeno, cicloalquilo de 3 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, NR^bR^c, arilo de 6 a 10 átomos de carbono, heteroarilo o heterociclilo. Esta modalidad es ilustrada por los compuestos de las fórmulas IB y IC:



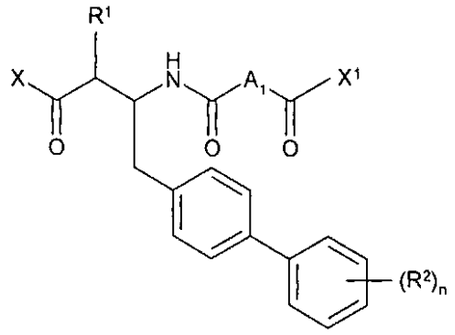
Fórmula IB



Fórmula IC

o una sal farmacéuticamente aceptable de los mismos, en donde X, R^1, R^2, B^1, R^3 tienen las definiciones de la fórmula I o I' anteriores; p es 0, 1, 2, 3 ó 4, y R^{2a} es halógeno.

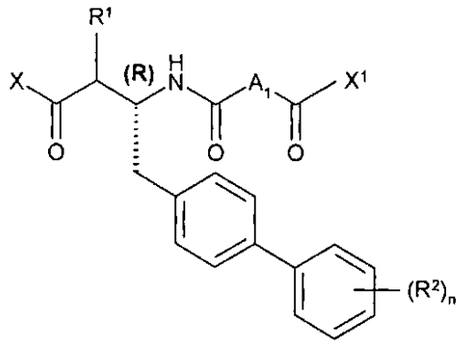
Ciertos compuestos de la fórmula I o I' incluyen los compuestos de la fórmula II:



Fórmula II

o una sal farmacéuticamente aceptable de los mismos, en donde X, X^1, A^1, R^1, R2 y n tienen las definiciones de la fórmula I o I' anteriores.

En una modalidad adicional, la invención pertenece a los compuestos de la fórmula II, en donde la estereoquímica del átomo de carbono que llevan los grupos bifenilo es (R). Esta modalidad es ilustrada por los compuestos de la fórmula IIA:

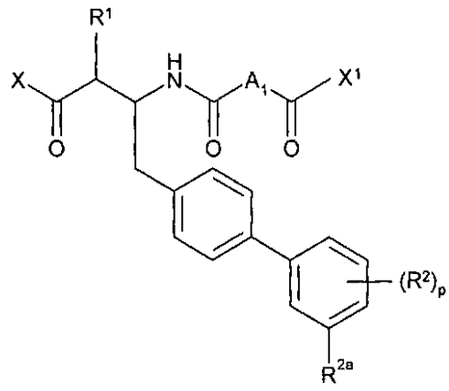


Fórmula IIA

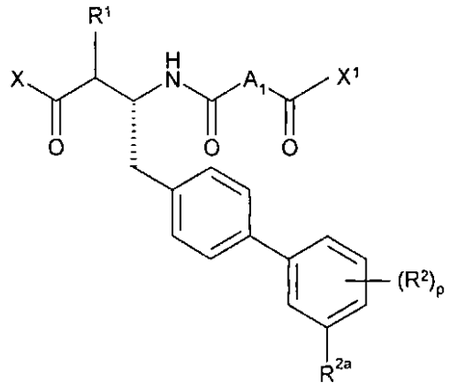
o una sal farmacéuticamente aceptable de los mismos, en donde X, X^1, A^1, R^1, R2 y n tienen las definiciones de la fórmula I o I'

anteriores.

Ciertos compuestos de la fórmula I, I' o II incluyen los compuestos de la fórmula IIB o IIC:



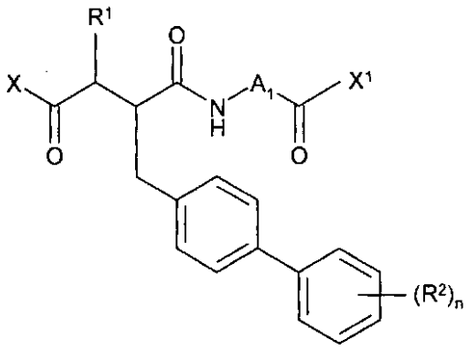
Fórmula IIB



Fórmula IIC

o una sal farmacéuticamente aceptable de los mismos, en donde X, X^1, A^1, R^1, R^2 tienen las definiciones de la fórmula I o I' anteriores; p es 0, 1, 2, 3 ó 4, y R^{2a} es halógeno.

Ciertos compuestos de la fórmula I o I' incluyen los compuestos de la fórmula III:



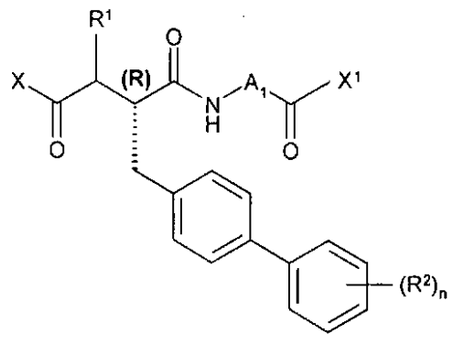
Fórmula III

o una sal farmacéuticamente aceptable de los mismos, en donde X, X^1, A^1, R^1, R2 y n tienen las definiciones de la fórmula I o I'

152

anteriores.

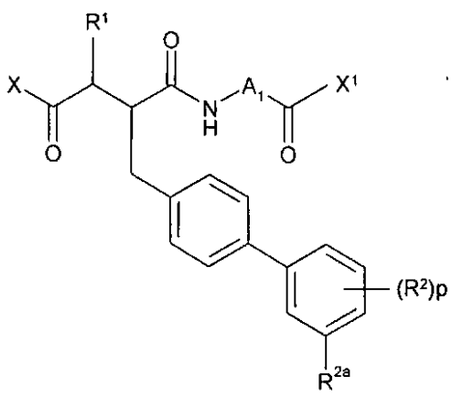
En una modalidad adicional, la invención pertenece a los compuestos de la fórmula III, en donde la estereoquímica del átomo de carbono que llevan los grupos bifenilo es (R). Esta modalidad es ilustrada por los compuestos de la fórmula IIIA:



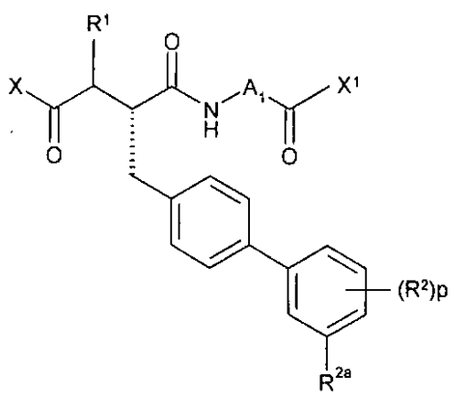
Fórmula IIIA

o una sal farmacéuticamente aceptable de los mismos, en donde X, X^1, A^1, R^1, R2 y n tienen las definiciones de la fórmula I o I' anteriores.

Ciertos compuestos de la fórmula III incluyen los compuestos de la fórmula IIIB o IIIC:



Fórmula IIIB

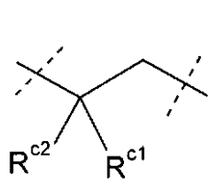


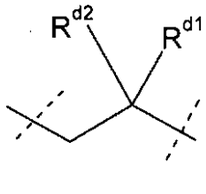
Fórmula IIIC

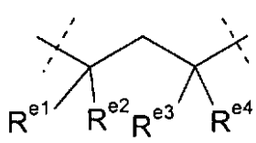
o una sal farmacéuticamente aceptable de los mismos, en donde X, X^1, A^1, R^1, R^2 tienen las definiciones de la fórmula I o I' anteriores; p es 0, 1, 2, 3 ó 4, y R^{2a} es halógeno.

En otra modalidad, la invención proporciona un compuesto de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, y III a IIIC, o de cualesquiera clases y sub-clases descritas en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, en donde A^1 es un alquileno lineal de 1 a 7 átomos de carbono, que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, O-acetato y cicloalquilo de 3 a 7 átomos de carbono; en donde dos grupos alquilo geminales pueden combinarse opcionalmente para formar un cicloalquilo de 3 a 7 átomos de carbono.

Una modalidad adicional incluye los compuestos de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, y III a IIIC, o de cualesquiera clases y sub-clases descritas en la presente, o una sal farmacéuticamente aceptable de los mismos, en donde A^1 es $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ o A^1 tiene las siguientes fórmulas:



,


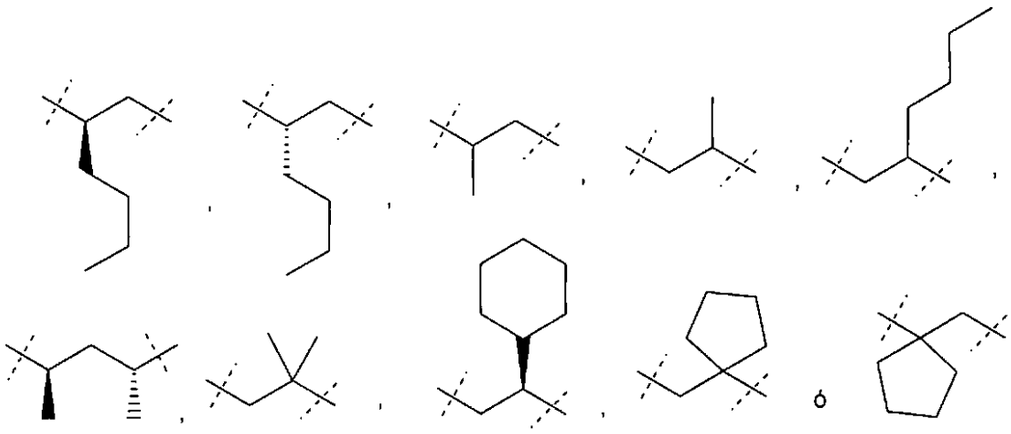
ó


.

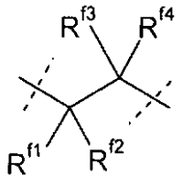
en donde R^{c1}, R^{c2}, R^{d1}, R^{d2}, R^{e1}, R^{e2}, R^{e3} y R^{e4} son

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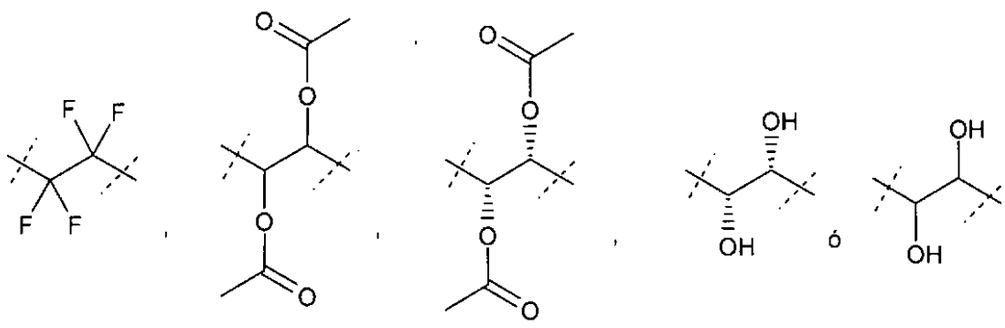
independientemente H, halógeno, C_{3-7}cicloalquilo, o alquilo de 1 a 7 átomos de carbono; y de una manera alternativa R^{c1} y R^{c2} o R^{d1} y R^{d2} pueden formar, junto con los átomos con los que están unidos, un cicloalquilo de 3 a 7 átomos de carbono. En un aspecto de esta modalidad, A^1 es uno de los siguientes:



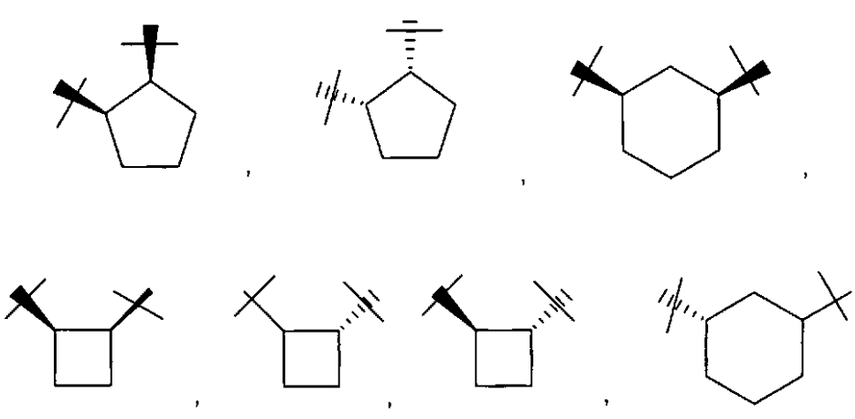
Todavía otra modalidad adicional incluye los compuestos de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, y III a IIIC, o de cualesquiera clases y sub-clases descritas en la presente, o una sal farmacéuticamente aceptable de los mismos, en donde A^1 tiene la siguiente fórmula:



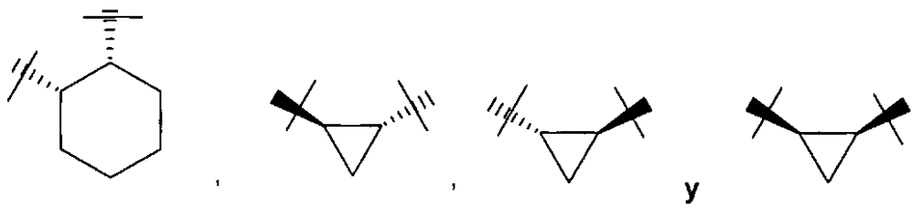
en donde R^{f1}, R^{f2}, R^{f3} y R^{f4} son independientemente H, halógeno, O-acetato o alquilo de 1 a 7 átomos de carbono. En una modalidad adicional, A^1 es uno de los siguientes:



En todavía otra modalidad, la invención proporciona un compuesto de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, y III a IIIC, o de cualesquiera clases y sub-clases descritas en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, en donde A^1 es un cicloalquilo de 3 a 7 átomos de carbono. Los ejemplos de esta modalidad, son los compuestos de cualquiera de las fórmulas I', I a IC, II a IIC, y III a IIIC, en donde A1 se selecciona a partir de los siguientes:



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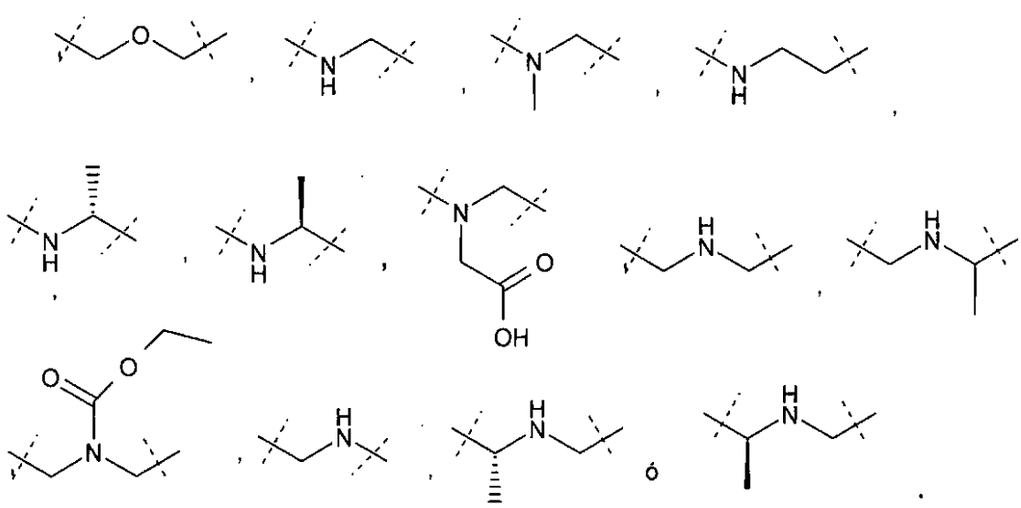


y

En todavía otra modalidad, la invención proporciona un compuesto de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, y III a IIIC, o de cualesquiera clases y sub-clases descritas en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, en donde A^1 es un alquenileno de 2 a 7 átomos de carbono lineal o ramificado. Un ejemplo de alquenileno de 2 a 7 átomos de carbono es *trans* CH=CH.

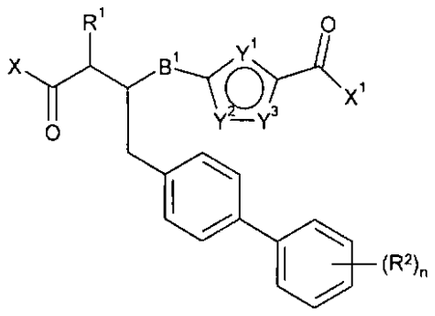
En todavía otra modalidad, la invención proporciona un compuesto de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, y III a IIIC, o de cualesquiera clases y sub-clases descritas en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, en donde A^1 es un alquileno lineal de 1 a 4 átomos de carbono, en donde uno o más átomos de carbono son reemplazados con un heteroátomo seleccionado a partir de O, NR^c; y A^1 está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno y alquilo de 1 a 7 átomos de carbono; en donde R^c por cada presentación, es independientemente H, alquilo de 1 a 7 átomos de carbono, -C(O)O-alquilo de 1 a 7 átomos de carbono, o $CH_2C(O)OH$. Una modalidad adicional incluye los compuestos de las fórmulas I', I

a IC, II a IIC, y III a IIIC, en donde A^1 es uno de los siguientes:



En todavía otra modalidad, la invención proporciona un compuesto de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, y III a IIIC, o de cualesquiera clases y sub-clases descritas en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, en donde A^1 es fenilo opcionalmente sustituido o heteroarilo, en donde los sustituyentes opcionales se definen como en la fórmula I o I'.

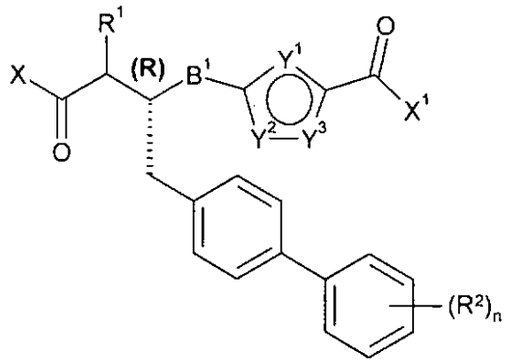
Ciertos compuestos de la modalidad anterior incluyen los compuestos de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, y III a IIIC, o una sal farmacéuticamente aceptable de los mismos, en donde A^1 es un anillo de heteroarilo de 5 miembros. Esta modalidad es ilustrada por los compuestos de la fórmula IV:



Fórmula IV

o una sal farmacéuticamente aceptable de los mismos, en donde X, X^1, B^1, R^1, R2 y n tienen las definiciones de la fórmula I o I' anteriores, e Y^1, Y^2 e Y^3 son independientemente N, NH, S, O o CH, y forman, junto con los átomos del anillo con el que están unidos, un anillo de heteroarilo de 5 miembros.

En un aspecto de esta modalidad, la invención pertenece a los compuestos de la fórmula IVA:

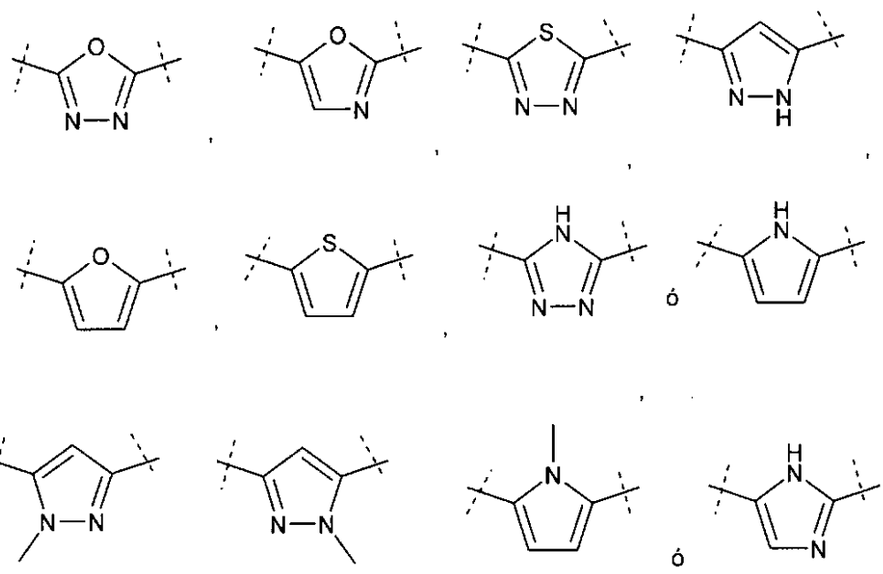


Fórmula IVA

o una sal farmacéuticamente aceptable de los mismos, en donde X, X^1, B^1, R^1, R^2, Y^1, Y^2, Y^3 y n tienen las definiciones de las fórmulas I, I' o IV anteriores.

En un aspecto de esta modalidad, Y^1, Y^2 e Y^3 forman, junto con

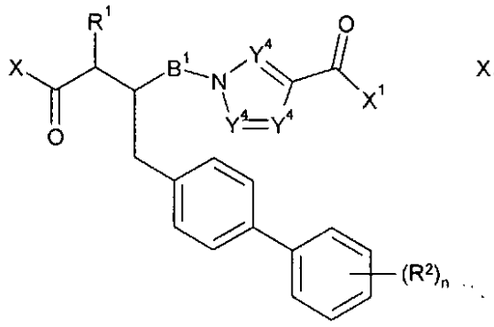
los átomos del anillo con el que están unidos, un anillo de heteroarilo de 5 miembros seleccionado a partir de furano, tiofeno, pirrol, pirazol, oxazol, tiazol, oxadiazol, tiadiazol, y triazol. Una modalidad adicional incluye los compuestos de la fórmula IV o VIA, o una sal farmacéuticamente aceptable de los mismos, en donde el heteroarilo de 5 miembros es uno de los siguientes:



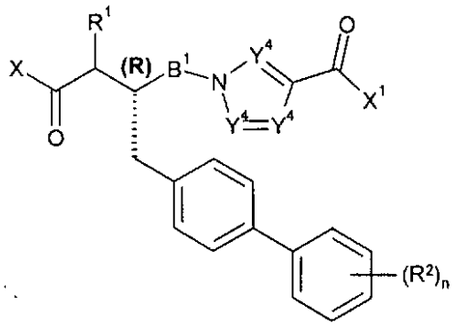
En una modalidad adicional, la invención pertenece a los compuestos de la fórmula IV o IVA, en donde n es 1, 2, 3, 4 ó 5; R^2 es halógeno en la posición meta, y los otros grupos R^2 opcionales son independientemente alquilo de 1 a 7 átomos de carbono, NO_2, CN, halógeno, cicloalquilo de 3 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, NR^bR^c, arilo de 6 a 10 átomos de carbono, heteroarilo o heterociclilo.

En todavía otro aspecto de la modalidad anterior, la invención

pertenece a los compuestos de la fórmula I', I a IC, II a IIC, o III a IIIC, o a una sal farmacéuticamente aceptable de los mismos, en donde A^1 es un anillo de heteroarilo de 5 miembros unido a la amida B^1 en un átomo de nitrógeno. Esta modalidad es ilustrada por los compuestos de las fórmulas V o VA:



Fórmula V

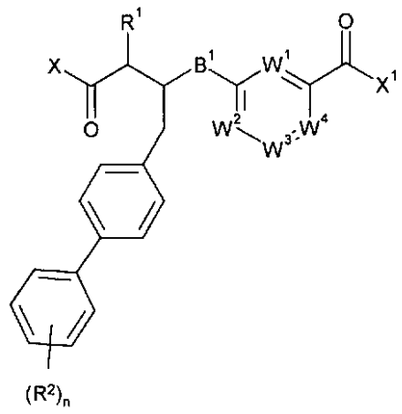


Fórmula VA

o una sal farmacéuticamente aceptable de los mismos, en donde X, X^1, B^1, R^1, R2 y n tienen las definiciones de la fórmula I o I' anteriores, y cada Y^4 es independientemente N, S, O o CH. En una modalidad adicional, la invención pertenece a los compuestos de la fórmula V o VA, en donde n es 1, 2, 3, 4 ó 5; R^2 es halógeno en la posición meta, y los otros grupos R^2 opcionales son independientemente alquilo de 1 a 7 átomos de carbono, NO_2, CN, halógeno, cicloalquilo de 3 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, NR^bR^c, arilo de 6 a 10 átomos de carbono, heteroarilo o heterociclilo.

En todavía otro aspecto de la modalidad anterior, la invención proporciona un compuesto de acuerdo con cualquiera de las fórmulas

I', I a IC, II a IIC, y III a IIIC, o de cualesquiera clases y sub-clases descritas en la presente, o una sal farmacéuticamente aceptable o un solvato del mismo, en donde A^1 es un fenilo o un anillo de heteroarilo de 6 miembros, en donde fenilo y heteroarilo están opcionalmente sustituidos con alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, NR^aR^b, $-OCH_2CO_2H$, u $-OCH_2C(O)NH_2$. Un aspecto de esta modalidad incluye los compuestos de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, y III a IIIC, o una sal farmacéuticamente aceptable de los mismos, en donde A^1 se conecta con la amida B^1 y con las fracciones $C(O)X^1$ en una configuración para. Otro aspecto de esta modalidad incluye los compuestos de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, y III a IIIC, en donde A^1 se conecta con la amida B^1 y con las fracciones $C(O)X^1$ en una configuración meta. Los compuestos de esta modalidad incluyen los compuestos de la fórmula VI:

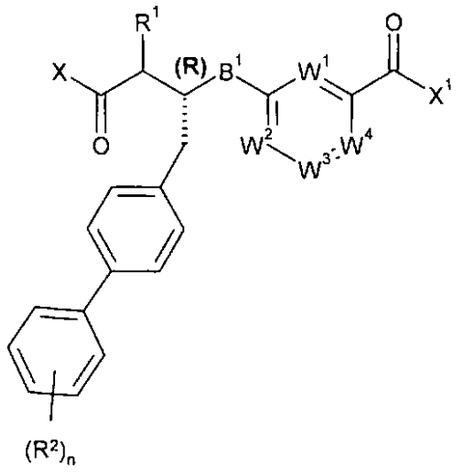


Fórmula VI

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o una sal farmacéuticamente aceptable de los mismos, en donde X, X^1, B^1, R^1, R2 y n tienen las definiciones de la fórmula I o I' anteriores, y W^1, W^2, W^3 y W^4 son independientemente N o CR^e, en donde cada R^e es independientemente H, alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, $-NR^aRb$, $-OCH_2CO_2H$ u $-OCH_2C(O)NH_2$. En un aspecto de esta modalidad, A^1 es fenilo, piridina o pirimidina.

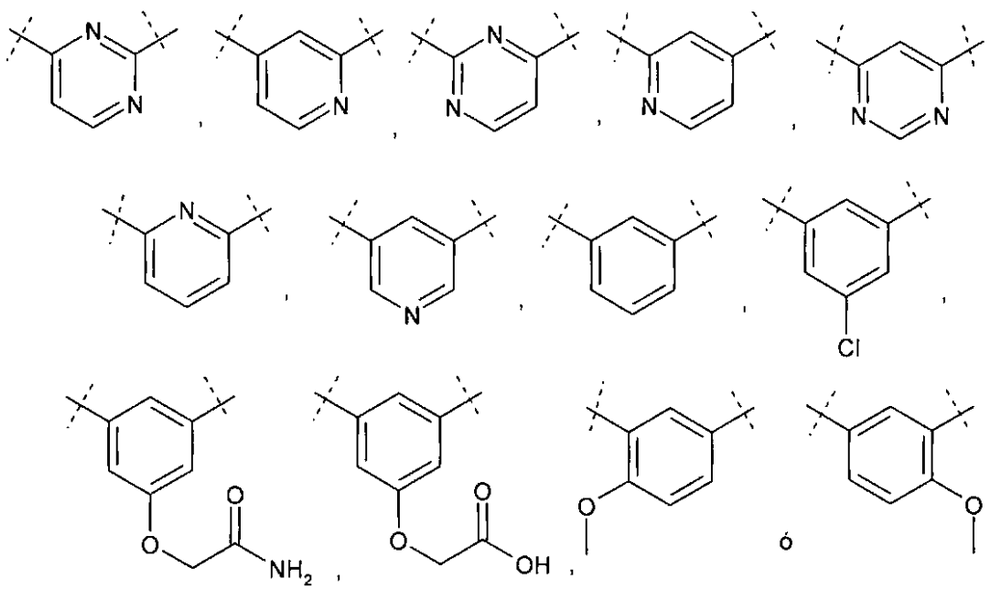
En una modalidad adicional, la invención pertenece a los compuestos de la fórmula VIA:



Fórmula VIA

o a una sal farmacéuticamente aceptable de los mismos, en donde X, X^1, B^1, R^1, R^2, W^1, W^2, W^3 y W^4 y n tienen las definiciones de las fórmulas I, I' o VI anteriores.

Una modalidad adicional incluye los compuestos de la fórmula VI o VIA, o una sal farmacéuticamente aceptable de los mismos, en donde A^1 es uno de los siguientes:

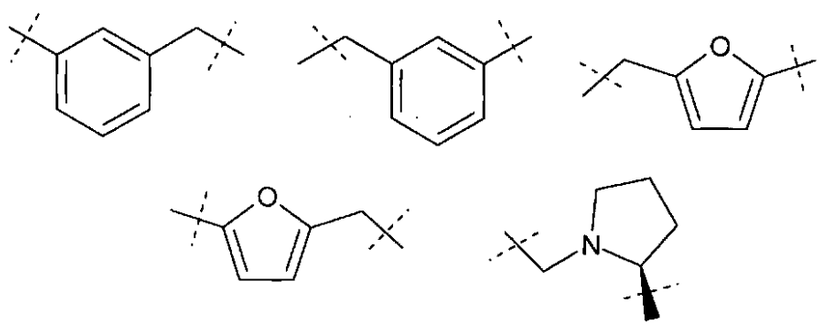


En una modalidad adicional, la invención pertenece a los compuestos de la fórmula VI o VIA, o a una sal farmacéuticamente aceptable de los mismos, en donde n es 1, 2, 3, 4 ó 5; R^2 es halógeno en la posición meta, y los otros grupos R^2 opcionales son independientemente alquilo de 1 a 7 átomos de carbono, NO_2, CN, halógeno, cicloalquilo de 3 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, NR^bR^c, arilo de 6 a 10 átomos de carbono, heteroarilo o heterociclilo.

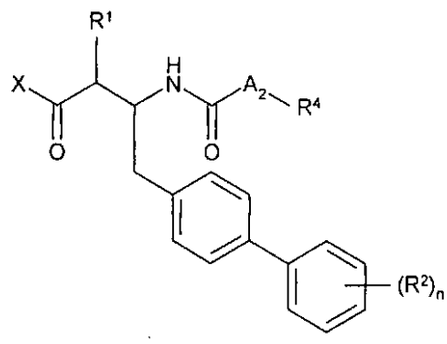
En un aspecto de la modalidad anterior, la invención pertenece a compuestos de acuerdo con cualquiera de las fórmulas I', I a IC, IV a IVC, V a VC, y VI a VIC, o a una sal farmacéuticamente aceptable de los mismos, en donde B^1 es -C(O)NH-. En otra modalidad, B^1 es -NHC(O)-.

Ciertos compuestos de la modalidad anterior incluyen los

compuestos de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, y III a IIIC, o una sal farmacéuticamente aceptable de los mismos, en donde A^1 es -alquileno de 1 a 4 átomos de carbono-arilo de 6 a 10 átomos de carbono-, -alquileno de 1 a 4 átomos de carbono-heteroaril- o -alquileno de 1 a 4 átomos de carbono-heterociclil-, -arilo de 6 a 10 átomos de carbono-alquileno de 1 a 4 átomos de carbono-, -heteroaril-alquileno de 1 a 4 átomos de carbono o –heterociclil-alquileno de 1 a 4 átomos de carbono-. En un aspecto de esta modalidad, A^1 es -alquileno de 1 a 4 átomos de carbono-arilo de 6 a 10 átomos de carbono-, -alquileno de 1 a 4 átomos de carbono-heteroaril- o -alquileno de 1 a 4 átomos de carbono-heterociclil-, en donde la porción de alquileno está unida al grupo amida B^1, y las fracciones de arilo, heteroarilo o heterociclilo están unidas a $C(O)X^1$. En otro aspecto de esta modalidad, A^1 es $-CH_2$-fenil- o -fenil-CH_2-. En otro aspecto de esta modalidad, A^1 es $-CH_2$-heteroarilo o –heteroaril-CH_2-. En una modalidad adicional, A^1 es $-CH_2$-heterociclilo o –heterociclil-CH_2-. Los ejemplos representativos de A^1 son los siguientes:

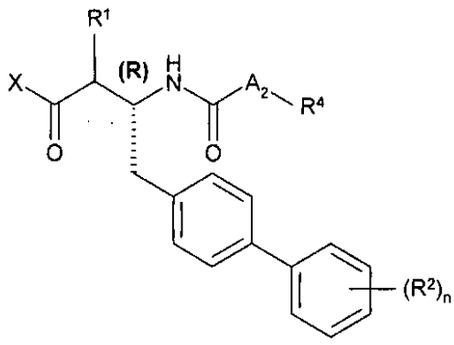


Ciertos compuestos de la fórmula I o I' incluyen los compuestos de la fórmula VII:



Fórmula VII

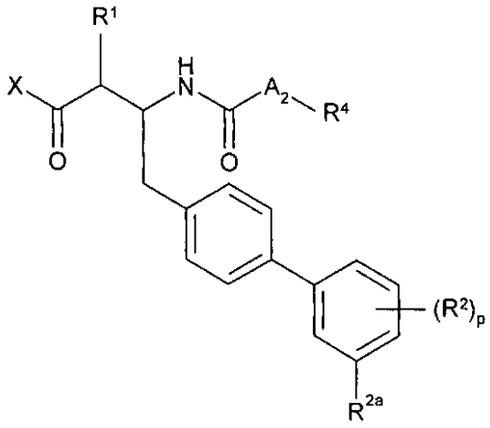
o una sal farmacéuticamente aceptable de los mismos, en donde X, A^2, R^1, R^2, R^4 y n tienen las definiciones de la fórmula I o I' anteriores. Una modalidad adicional incluye los compuestos de la fórmula VIIA:



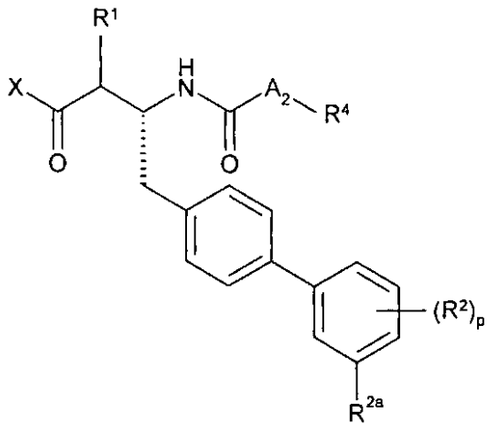
Fórmula VIIA

o una sal farmacéuticamente aceptable de los mismos, en donde X, A^2, R^1, R^2, R^4 y n tienen las definiciones de la fórmula I o I' anteriores.

Ciertos compuestos de la fórmula VII o VIIA tienen la fórmula VIIB o VIIC:



Fórmula VIIB



Fórmula VIIC

o una sal farmacéuticamente aceptable de los mismos, en donde X, A^2, R^1, R^2, R^4 tienen las definiciones de la fórmula I o I' anteriores; p es 0, 1, 2, 3 ó 4, y R^{2a} es halógeno.

Un aspecto adicional de esta modalidad incluye los compuestos de acuerdo con cualquiera de las fórmulas VII a VIIC, o una sal farmacéuticamente aceptable de los mismos, en donde A^2 es $(CH_2)_p$ y p es 0, 1, 2, 3. En un aspecto de esta modalidad, p es 0, por consiguiente A^2 es un enlace. En otro aspecto de esta modalidad, A^2 es CH_2 o CH_2-CH_2.

En otro aspecto de esta modalidad, la invención proporciona los compuestos de acuerdo con cualquiera de las fórmulas VII a VIIC, o una sal farmacéuticamente aceptable de los mismos, en donde R^4 arilo de 6 a 10 átomos de carbono opcionalmente sustituido. Los ejemplos representativos de arilo son benzo-imidazolona, benzo-isotiazolona o fenilo. En un aspecto adicional de esta modalidad, R^4 es fenilo. Los sustituyentes sobre el anillo de

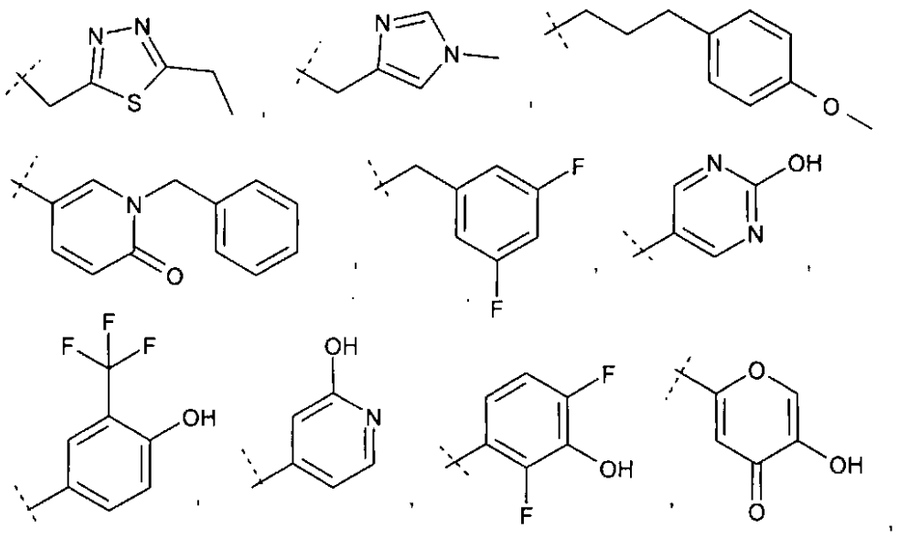
fenilo incluyen, por ejemplo, halógeno (por ejemplo, F, Cl), hidroxilo, halo-alquilo de 1 a 7 átomos de carbono (por ejemplo, CF_3), $-NHS(O)_2$-alquilo de 1 a 7 átomos de carbono, heteroarilo, alcoxilo de 1 a 7 átomos de carbono o alquilo de 1 a 7 átomos de carbono.

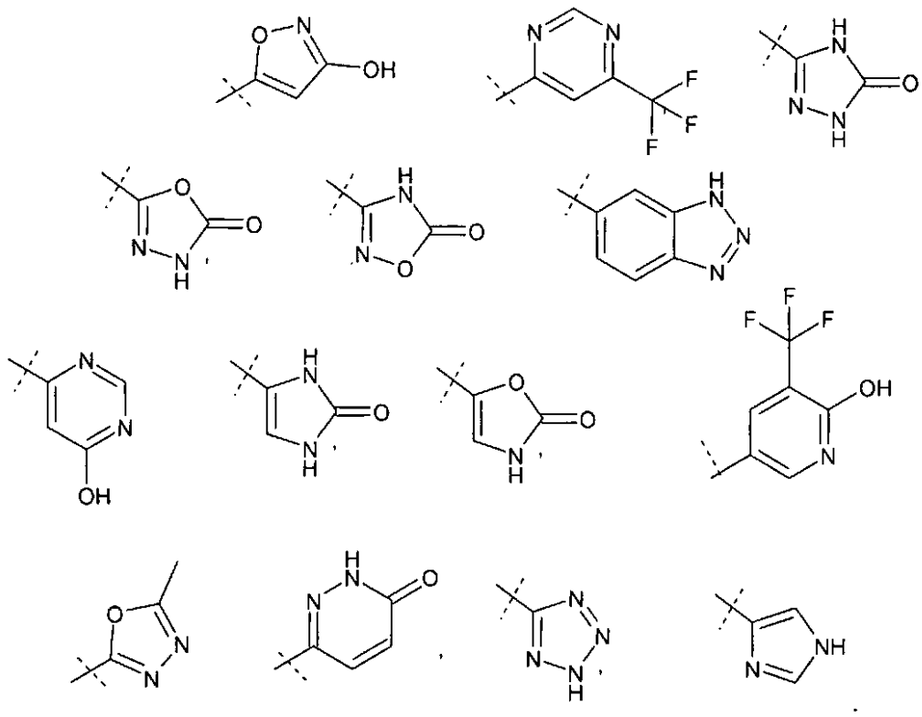
En todavía otro aspecto de esta modalidad, la invención proporciona los compuestos de acuerdo con cualquiera de las fórmulas VII a VIIC, o una sal farmacéuticamente aceptable de los mismos, en donde R^4 es un heteroarilo bicíclico opcionalmente sustituido.

En todavía otro aspecto de esta modalidad, la invención proporciona los compuestos de acuerdo con cualquiera de las fórmulas VII a VIIC, o una sal farmacéuticamente aceptable de los mismos, en donde R^4 es heteroarilo de 5 ó 6 miembros opcionalmente sustituido. En un aspecto de esta modalidad, R^4 es un anillo de heteroarilo de 6 miembros seleccionado a partir del grupo que consiste en pirazinilo, piridinilo, pirimidinilo, oxo-piranilo (por ejemplo, piranona, piran-4-ona opcionalmente sustituida, piran-2-ona tal como 3-hidroxi-piran-4-ona, 3-hidroxi-piran-2-ona), y oxo-piridinilo (por ejemplo, piridinona, piridin-4-ona o piridin-2-ona opcionalmente sustituidas, tales como, por ejemplo 3-hidroxi-1-metil-piridin-4-ona o 1-bencil-piridin-2-ona), o pirimidinona (es decir, oxo-pirimidinilo). En otro aspecto de esta modalidad, R^4 es un anillo de heteroarilo de 5 miembros seleccionado a partir del grupo que consiste en oxazol, pirrol, pirazol, iso-oxazol, triazol, tetrazol, oxadiazol (por ejemplo, 1-oxa-3,4-diazol, 1-oxa-2,4-diazol), oxadiazolona (por ejemplo,

oxadiazol-2-ona), tiazol, isotiazol, tiofeno, imidazol y tiadiazol. Otros ejemplos representativos de R^4 son oxazolona, tiazolona, oxadiazolona, triazolona, oxazolona, imidazolona, pirazolona. En una modalidad adicional, los sustituyentes opcionales sobre arilo y heteroarilo de 6 a 10 átomos de carbono, se seleccionan a partir de hidroxilo, alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno, halo-alquilo de 1 a 7 átomos de carbono o bencilo.

En todavía otro aspecto de la modalidad anterior, la invención proporciona los compuestos de acuerdo con cualquiera de las fórmulas VII a VIIC, o una sal farmacéuticamente aceptable de los mismos, en donde R^4 es un heteroarilo bicíclico. Una modalidad adicional incluye los compuestos de acuerdo con cualquiera de las fórmulas VII a VIIC, o una sal farmacéuticamente aceptable de los mismos, en donde R^4 es indol, benzotiazol o bencimidazol. Los ejemplos representativos de R^4 son los siguientes:





En todavía otro aspecto de la modalidad anterior, la invención proporciona los compuestos de acuerdo con cualquiera de las fórmulas VII a VIIC, o una sal farmacéuticamente aceptable de los mismos, en donde R^4 es a heterociclilo monocíclico saturado o parcialmente saturado, cuyo heterociclilo contiene cuando menos un heteroátomo seleccionado a partir de nitrógeno, azufre y oxígeno, y cuyo heterociclilo está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en oxo, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, heteroarilo,

-$NHSO_2$-alquilo de 1 a 7 átomos de carbono y bencilo. En un aspecto particular de esta modalidad, R^4 es pirrolidina o imidazolidina, en donde el heterociclilo puede estar enlazado a la fracción de carbonilo ($C(O)$-A^2) por medio de un átomo de carbono o un átomo de nitrógeno, y el heterociclilo está opcionalmente sustituido con oxo.

En una modalidad, la invención proporciona los compuestos de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, III a IIIC, IV, IVA, V, VA, VI, VIA, y VII a VIIC, o una sal farmacéuticamente aceptable de los mismos, en donde R^1 es H.

En otra modalidad, la invención proporciona los compuestos de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, III a IIIC, IV, IVA, V, VA, VI, VIA, y VII a VIIC, o una sal farmacéuticamente aceptable de los mismos, en donde cada R^2 es independientemente halógeno, alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, halo-alquilo de 1 a 7 átomos de carbono, y n es 0, 1 ó 2. En una modalidad adicional n es 1, 2, 3, 4 ó 5, R^2 es halógeno en la posición meta, y los otros grupos R^2 opcionales son independientemente halógeno, alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxilo o halo-alquilo. En todavía una modalidad adicional, la invención proporciona los compuestos de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, III a IIIC, IV, IVA, V, VA, VI, VIA, y VII a VIIC, o una sal farmacéuticamente aceptable de los mismos, en donde n es 1 ó 2, R^2 es meta-cloro o meta-fluoro y el otro grupo R^2 opcional es halógeno, alquilo de 1 a 7 átomos de carbono, alcoxilo

de 1 a 7 átomos de carbono, hidroxilo o halo-alquilo.

En todavía otra modalidad, la invención proporciona los compuestos de acuerdo con cualquiera de las fórmulas I', I a IC, II a IIC, III a IIIC, I, IVA, V, VA, VI, VIA, y VII a VIIC, o una sal farmacéuticamente aceptable de los mismos, en donde X y X^1 son independientemente OH u -O-alquilo de 1 a 7 átomos de carbono (por ejemplo, –O-etilo, –O-metilo, o –O-n-butilo). En un aspecto particular de esta modalidad, X y X^1 son OH. En otro aspecto de esta modalidad, X y X^1 son independientemente -O-alquilo de 1 a 7 átomos de carbono, en donde el alquilo está sustituido con arilo de 6 a 10 átomos de carbono, heteroarilo, heterociclilo, $C(O)NH_2$, C(O)NH-alquilo de 1 a 6 átomos de carbono, o C(O)N(alquilo de 1 a 6 átomos de carbono)$_2$. Los ejemplos representativos de X o X^1 son $–O-CH_2-C(O)N(CH_3)_2$, $-O-CH_2-CH_2$-morfolina, $-O-CH_2$-dioxolona u -O-bencilo. En todavía otro aspecto de esta modalidad, X y X^1 son –O-arilo de 6 a 10 átomos de carbono. A los ejemplos representativos de –O-arilo de 6 a 10 átomos de carbono es -O-(2,3-dihidro-1H-indeno).

En otra modalidad, los grupos X, X^1, B^1, A^1, A^2, R^2, R^1 y R^4 son aquéllos definidos por los grupos X, X^1, A^1, A^2, B^1, R^2, R^1 y R^4 en la sección de Ejemplos más adelante.

En otra modalidad, los compuestos individuales de acuerdo con la invención son aquéllos enlistados en la sección de Ejemplos más adelante, o una sal farmacéuticamente aceptable de los mismos.

Definiciones

Para los propósitos de interpretar esta memoria descriptiva, se

(67)

aplicarán las siguientes definiciones a menos que se especifique de otra manera y siempre que sea apropiado, los términos empleados en el singular también incluirán el plural y *viceversa*.

Como se utiliza en la presente, el término "alquilo" se refiere a una fracción de hidrocarburo ramificada o no ramificada completamente saturada (o de cadena recta o lineal) que comprende de 1 a 20 átomos de carbono. De preferencia el alquilo comprende de 1 a 7 átomos de carbono, y de una manera muy preferible de 1 a 4 átomos de carbono. Los ejemplos representativos de alquilo incluyen metilo, etilo, propilo normal, *iso*-propilo, butilo normal, butilo secundario, isobutilo, butilo terciario, pentilo normal, isopentilo, neopentilo, hexilo normal, 3-metil-hexilo, 2,2-dimetil-pentilo, 2,3-dimetil-pentilo, *n*-heptilo. El término "alquilo C_{1-7}" se refiere a un hidrocarburo que tiene de uno a siete átomos de carbono. Más aún, el término alquenilo incluye tanto "alquilos insustituidos" como "alquilos sustituidos". El término "alquileno" se refiere a un radical de alquilo divalente, en donde alquilo es como se define anteriormente.

El término "alquenilo" se refiere a un hidrocarburo ramificado o no ramificado que tiene cuando menos un doble enlace de carbono-carbono. El término "alquenilo C_{2-7}" se refiere a un hidrocarburo que tiene de dos a siete átomos de carbono, y el cual comprende cuando menos un doble enlace de carbono-carbono. Los ejemplos representativos de alquenilo son vinilo, prop-1-enilo, alilo, butenilo, isopropenilo o isobutenilo. El término "alquileno" se refiere a un radical de alquenilo divalente, en donde el alquenilo es como se

define anteriormente.

Como se utiliza en la presente, el término "halo-alquilo" se refiere a un alquilo como se define en la presente, que está sustituido por uno o más grupos halógeno como se definen en la presente. De preferencia el halo-alquilo puede ser mono-halo-alquilo, di-halo-alquilo o poli-halo-alquilo incluyendo per-halo-alquilo. Un mono-halo-alquilo puede tener un átomo de yodo, bromo, cloro o flúor dentro del grupo alquilo. Los grupos di-halo-alquilo y poli-halo-alquilo pueden tener dos o más de los mismos átomos de halógeno, o una combinación de diferentes grupos halógeno dentro del alquilo. De preferencia, el polihalo-alquilo contiene hasta 12, ó 10, u 8, ó 6, ó 4, ó 3, ó 2 grupos halógeno. Los ejemplos representativos de halo-alquilo son fluoro-metilo, di-fluoro-metilo, tri-fluoro-metilo, cloro-metilo, di-cloro-metilo, tri-cloro-metilo, penta-fluoro-etilo, hepta-fluoro-propilo, di-fluoro-cloro-metilo, di-cloro-fluoro-metilo, di-fluoro-etilo, di-fluoro-propilo, di-cloro-etilo y di-cloro-propilo. Un perhalo-alquilo se refiere a un alquilo que tiene todos los átomos de hidrógeno reemplazados con átomos de halógeno. El término "halo-alquilo C_{1-7}" se refiere a un hidrocarburo que tiene de uno a siete átomos de carbono, y que está sustituido por uno o más grupos halógeno.

Como se utiliza en la presente, el término "alcoxilo" se refiere a alquil-O-, en donde el alquilo se define anteriormente en la presente. Los ejemplos representativos de alcoxilo incluyen, pero no se limitan a, metoxilo, etoxilo, propoxilo, 2-propoxilo, butoxilo,

terbutoxilo, pentiloxilo, hexiloxilo, ciclopropiloxi-, ciclohexiloxi- y similares. De preferencia, los grupos alcoxilo tienen de aproximadamente 1 a 7, más preferiblemente de aproximadamente 1 a 4 átomos de carbono.

Como se utiliza en la presente, el término "cicloalquilo" se refiere a grupos hidrocarburo monocíclicos, bicíclicos o tricíclicos, saturados o insaturados, pero no aromáticos, de 3 a 12 átomos de carbono, de preferencia de 3 a 8 ó de 3 a 7 átomos de carbono. Para el sistema de cicloalquilo bicíclico y tricíclico, todos los anillos son no aromáticos. Los grupos hidrocarburo monocíclicos de ejemplo incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclohexilo y ciclohexenilo. Los grupos hidrocarburo bicíclicos de ejemplo incluyen bornilo, decahidro-naftilo, biciclo-[2.1.1]-hexilo, biciclo-[2.2.1]-heptilo, biciclo-[2.2.1]-heptenilo, biciclo-[2.2.2]-octilo. Los grupos hidrocarburo tricíclicos de ejemplo incluyen adamantilo. El término "cicloalquilo C_{3-7}" se refiere a los grupos hidrocarburo cíclicos que tienen de 3 a 7 átomos de carbono. El término "cicloalquil-alquilo" se refiere a un alquilo sustituido con cicloalquilo.

El término "arilo" se refiere a los grupos hidrocarburo aromático monocíclicos o bicíclicos que tienen de 6 a 10 átomos de carbono en la porción del anillo. El término "arilo" también se refiere a un grupo en donde el anillo aromático está fusionado con un anillo de cicloalquilo, en donde el radical de unión está sobre el anillo aromático o sobre el anillo de cicloalquilo fusionado. Los ejemplos representativos de arilo son fenilo, naftilo, hexahidro-indilo, indanilo

o tetrahidro-naftilo. El término "arilo C_{6-10}" se refiere a los grupos hidrocarburo aromáticos que tienen de 6 a 10 átomos de carbono en la porción del anillo.

El término "aril-alquilo" es un alquilo sustituido con arilo. Los ejemplos representativos de aril-alquilo son bencilo o fenil-CH_2CH_2-. El término también incluye la fracción de aril-alquilo sustituida.

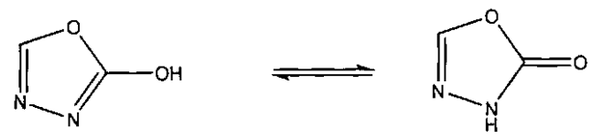
El término "heteroarilo" incluye heteroarilo monocíclico o bicíclico, que contiene de 5 a 10 miembros del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, y cada heteroátomo se selecciona independientemente a partir de O, N o S, en donde S y N puede estar oxidados hasta diferentes estados de oxidación. Para el sistema de heteroarilo bicíclico, el sistema es completamente aromático (es decir, todos los anillos son aromáticos).

Los grupos heteroarilo monocíclicos típicos incluyen tienilo, furilo, pirrolilo, imidazolilo, pirazolilo, tiazolilo, isotiazolilo, oxa-2,3-diazolilo, oxa-2,4-diazolilo, oxa-2,5-diazolilo, oxa-3,4-diazolilo, tia-2,3-diazolilo, tia-2,4-diazolilo, tia-2,5-diazolilo, tia-3,4-diazolilo, 3-, 4-, ó 5-isotiazolilo, 2-, 4-, ó 5-oxazolilo, 3-, 4-, ó 5-isoxazolilo, 3- ó 5-1,2,4-triazolilo, 4- ó 5-1,2, 3-triazolilo, tetrazolilo, 2-, 3-, ó 4-piridilo, 3- o 4-piridazinilo, 3-, 4-, ó 5-pirazinilo, 2-pirazinilo, 2-, 4-, ó 5-pirimidinilo.

El término "heteroarilo" también se refiere a un grupo en donde un anillo heteroaromático se fusiona con uno o más anillos de arilo, cicloalifáticos, o heterociclilos, en donde el radical o el punto de

unión está sobre el anillo heteroaromático o sobre el anillo de arilo fusionado. Los ejemplos representativos de heteroarilo bicíclico son indolilo, isoindolilo, indazolilo, indolizinilo, purinilo, quinolizinilo, quinolinilo, isoquinolinilo, cinolinilo, ftalazinilo, naftiridinilo, quinazolinilo, quinaxalinilo, tieno-[2,3-b]furanilo, furo-[3,2-b]-piranilo, 5H-pirido-[2,3-d]-o-oxazinilo, 1H-pirazolo-[4,3-d]-oxazolilo, 4H-imidazo-[4,5-d]-tiazolilo, pirazino-[2,3-d]-piridazinilo, imidazo-[2,1-b]-tiazolilo, imidazo-[1,2-b][1,2,4]-triazinilo, 7-benzo-[b]-tienilo, benzoxazolilo, bencimidazolilo, benzotiazolilo, benzoxapinilo, benzoxazinilo, 1H-pirrolo-[1,2-b][2]-benzazapinilo, benzo-furilo, benzo-tiofenilo, benzo-triazolilo, pirrolo-[2,3-b]-piridinilo, pirrolo-[3,2-c]-piridinilo, pirrolo-[3,2-c]-piridinilo, pirrolo-[3,2-b]-piridinilo, imidazo-[4,5-b]-piridinilo, imidazo-[4,5-c]-piridinilo, pirazolo-[4,3-d]-piridinilo, pirazolo-[4,3-c]-piridinilo, pirazolo-[3,4-c]-piridinilo, pirazolo-[3,4-d]-piridinilo, pirazolo-[3,4-b]-piridinilo, imidazo-[1,2-a]-piridinilo, pirazolo-[1,5-a]-piridinilo, pirrolo-[1,2-b]-piridazinilo, imidazo-[1,2-c]-pirimidinilo, pirido-[3,2-d]-pirimidinilo, pirido-[4,3-d]-pirimidinilo, pirido-[3,4-d]-pirimidinilo, pirido-[2,3-d]-pirimidinilo, pirido-[2,3-b]-pirazinilo, pirido-[3,4-b]-pirazinilo, pirimido-[5,4-d]-pirimidinilo, pirazino-[2,3-b]-pirazinilo, o pirimido-[4,5-d]-pirimidinilo.

Cuando una fracción de heteroarilo está sustituida con hidroxilo, la invención también pertenece a su oxo tautomérico. Por ejemplo, un oxadiazol sustituido con hidroxilo también incluye oxo-oxadiazol, o también conocido como oxadiazolona. La tautomerización se representa como sigue:



Como se utiliza en la presente, el término "heterociclilo" o "heterociclo" se refiere a un anillo no aromático opcionalmente sustituido, saturado o insaturado (parcialmente insaturado), el cual es un monocíclico de 4, 5, 6, ó 7 miembros, y contiene cuando menos un heteroátomo seleccionado a partir de O, S y N, en donde los átomos de N y S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación. Para el sistema de anillo de heterociclilo bicíclico y tricíclico, un sistema de anillo no aromático se define como un sistema de anillo no completamente o parcialmente insaturado. Por consiguiente los sistemas de anillos de heterociclilo bicíclicos y tricíclicos incluyen los sistemas de anillos de heterociclilo en donde uno de los anillos fusionados es aromático, pero los otros son no aromáticos. En una modalidad, la fracción de heterociclilo representa un anillo monocíclico saturado que contiene de 5 a 7 átomos del anillo, y que contiene opcionalmente un heteroátomo adicional seleccionado a partir de O, S o N. El grupo heterocíclico se puede unir en un heteroátomo o en un átomo de carbono. El heterociclilo puede incluir anillos fusionados o puenteados, así como anillos espirocíclicos. Los ejemplos de los heterociclos incluyen dihidro-furanilo, dioxolanilo, dioxanilo, ditianilo, piperazinilo, pirrolidina, dihidro-piranilo, oxatiolanilo, ditiolano, oxatianilo, tiomorfolino, oxiranilo, aziridinilo, oxetanilo, oxepanilo,

azetidinilo, tetrahidro-furanilo, tetrahidro-tiofenilo, pirrolidinilo, tetrahidro-piranilo, piperidinilo, morfolino, piperazinilo, azepinilo, oxapinilo, oxa-azepanilo, oxatianilo, tiepanilo, azepanilo, dioxepanilo, y diazepanilo.

El término "hidroxi-alquilo" se refiere a los grupos alquilo, como se describen anteriormente, en donde el grupo alquilo está sustituido con uno o más hidroxilos.

El término "halógeno" incluye flúor, bromo, cloro y yodo. El término "perhalogenado" se refiere en términos generales a una fracción en donde todos los hidrógenos son reemplazados por átomos de halógeno.

El término "heteroátomo" incluye los átomos de cualquier elemento diferente de carbono o hidrógeno. Los heteroátomos preferidos son nitrógeno, oxígeno, azufre y fósforo. En otra modalidad, el heteroátomo es nitrógeno, oxígeno o azufre.

Se observará que la estructura de algunos de los compuestos de esta invención incluye átomos de carbono asimétricos. De conformidad con lo anterior, se debe entender que los isómeros que se presenten a partir de tal asimetría (por ejemplo, todos los enantiómeros y diaestereómeros) se incluyen dentro del alcance de esta invención, a menos que se indique de otra manera. Estos isómeros se pueden obtener en una forma sustancialmente pura mediante las técnicas de separación clásicas y mediante síntesis estereoquímicamente controlada. Adicionalmente, las estructuras y otros compuestos y fracciones discutidos en esta solicitud también

incluyen todos los tautómeros de los mismos.

Como se utiliza en la presente, el término "isómeros" se refiere a diferentes compuestos que tienen la misma forma molecular pero difieren en el arreglo y configuración de los átomos. También como se utiliza en la presente, el término "un isómero óptico" o "un estereoisómero" se refiere a cualquiera de las diferentes configuraciones estereoisoméricas que puedan existir para un compuesto dado de la presente invención, e incluye los isómeros geométricos. Se entiende que un sustituyente se puede unir en un centro quiral de un átomo de carbono. Por consiguiente, la invención incluye los enantiómeros, diaestereómeros o racematos del compuesto. Los "enantiómeros" son un par de estereoisómeros que son imágenes de espejo que no se pueden sobreponer uno del otro. Una mezcla de 1:1 de un par de enantiómeros es una mezcla "racémica". El término se utiliza para designar una mezcla racémica donde sea apropiado. Los "diaestereoisómeros" son los estereoisómeros que tienen cuando menos dos átomos asimétricos, pero que no son imágenes de espejo uno del otro. La estereoquímica absoluta se especifica de acuerdo con el sistema de Cahn-Ingold-Prelog R-S. Cuando un compuesto es un enantiómero puro, la estereoquímica en cada átomo de carbono quiral se puede especificar mediante *R* o *S*. Los compuestos resueltos cuya configuración absoluta se desconozca, se pueden designar como (+) o (-), dependiendo de la dirección (dextrógira o levógira) en la que gire la luz polarizada en el plano a la longitud de onda de la línea D

de sodio. Algunos de los compuestos descritos en la presente contienen uno o más centros o ejes asimétricos, y por lo tanto, pueden dar lugar a enantiómeros, diaestereómeros, y otras formas estereoisoméricas que puedan definirse, en términos de estereoquímica absoluta, como (*R*) o (*S*). La presente invención pretende incluir todos los posibles isómeros, incluyendo las mezclas racémicas, las formas ópticamente puras, y las mezclas de intermediarios. Los isómeros (R) y (S) ópticamente activos se pueden preparar utilizando sintones quirales o reactivos quirales, o se pueden resolver empleando técnicas convencionales. Si el compuesto contiene un doble enlace, el sustituyente puede estar en la configuración E ó Z. Si el compuesto contiene un cicloalquilo disustituido, el sustituyente de cicloalquilo puede tener una configuración *cis* o *trans*. También se pretende incluir a todas las formas tautoméricas.

Cualquier átomo asimétrico (por ejemplo, carbono, o similares) de los compuestos de la presente invención, puede estar presente en una configuración racémica o enantioméricamente enriquecida, por ejemplo en la configuración (R), (S) o (R,S). En ciertas modalidades, cada átomo asimétrico tiene un exceso enantiomérico de cuando menos el 50 por ciento, un exceso enantiomérico de cuando menos el 60 por ciento, un exceso enantiomérico de cuando menos el 70 por ciento, un exceso enantiomérico de cuando menos el 80 por ciento, un exceso enantiomérico de cuando menos el 90 por ciento, un exceso enantiomérico de cuando menos el 95 por ciento, o un exceso

enantiomérico de cuando menos el 99 por ciento en la configuración (R) o (S). Los sustituyentes en átomos con enlaces insaturados, si es posible, pueden estar presentes en la forma *cis* (Z) o *trans* (E).

De conformidad con lo anterior, como se utiliza en la presente, un compuesto de la presente invención puede estar en la forma de uno de los posibles isómeros, rotámeros, atropisómeros, tautómeros o mezclas de los mismos, por ejemplo, como isómeros geométricos (*cis* o *trans*), diaestereómeros, isómeros ópticos (antípodas), o racematos sustancialmente puros o mezclas de los mismos.

Cualesquiera mezclas de isómeros resultantes se pueden separar con base en las diferencias fisicoquímicas de los constituyentes, en los isómeros geométricos u ópticos puros o sustancialmente puros, diaestereómeros, racematos, por ejemplo mediante cromatografía y/o cristalización fraccionaria.

Cualesquiera racematos resultantes de los productos finales o de los intermediarios se pueden resolver en los antípodas ópticos mediante métodos conocidos, por ejemplo mediante la separación de las sales diaestereoméricas de los mismos, obtenidas con un ácido o base ópticamente activos, y liberando el compuesto ácido o básico ópticamente activo. En particular, se puede emplear una fracción básica de esta manera para resolver los compuestos de la presente invención en sus antípodas ópticos, por ejemplo mediante cristalización fraccionaria de una sal formada con un ácido ópticamente activo, por ejemplo, ácido tartárico, ácido dibenzoil-tartárico, ácido diacetil-tartárico, ácido di-O,O'-p-toluoil-tartárico,

ácido mandélico, ácido málico, o ácido canfor-10-sulfónico. Los productos racémicos también se pueden resolver mediante cromatografía quiral, por ejemplo cromatografía de líquidos a alta presión (HPLC) utilizando un adsorbente quiral.

Como se utiliza en la presente, el término "sales farmacéuticamente aceptables" se refiere a las sales que retienen la efectividad biológica y las propiedades de los compuestos de esta invención, y que típicamente no son biológicamente o de otra manera indeseables. En muchos casos, los compuestos de la presente invención son capaces de formar sales de ácido y/o de base en virtud de la presencia de grupos amino y/o carboxilo, o grupos similares a los mismos.

Las sales de adición de ácido farmacéuticamente aceptables se pueden formar con ácidos inorgánicos y ácidos orgánicos, por ejemplo, las sales de acetato, aspartato, benzoato, besilato, bicarbonato/carbonato, bisulfato/sulfato, borato, camsilato, citrato, edisilato, esilato, formato, fumarato, gluceptato, gluconato, glucuronato, hexafluorofosfato, dibenzoato, clorhidrato/cloruro, bromhidrato/bromuro, yodhidrato/yoduro, isetionato, lactato, malato, maleato, malonato, mesilato, metil-sulfato, naftilato, 2-napsilato, nicotinato, nitrato, orotato, oxalato, palmitato, pamoato, fosfato/fosfato ácido/fosfato diácido, sacarato, estearato, succinato, tartrato, tosilato y trifluoro-acetato. Los ácidos inorgánicos a partir de los cuales se pueden derivar las sales incluyen, por ejemplo, ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico,

ácido fosfórico, y similares. Los ácidos orgánicos a partir de los cuales se pueden derivar las sales incluyen, por ejemplo, ácido acético, ácido propiónico, ácido glicólico, ácido pirúvico, ácido oxálico, ácido maleico, ácido malónico, ácido succínico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido cinámico, ácido mandélico, ácido metan-sulfónico, ácido etan-sulfónico, ácido p-toluen-sulfónico, ácido salicílico, y similares. Las sales de adición de base farmacéuticamente aceptables se pueden formar con bases inorgánicas y orgánicas. Las bases inorgánicas a partir de las cuales se pueden derivar las sales incluyen, por ejemplo, sodio, potasio, litio, amonio, calcio, magnesio, hierro, zinc, cobre, manganeso, aluminio, y similares; se prefieren en particular las sales de amonio, potasio, sodio, calcio y magnesio. Las bases orgánicas a partir de las cuales se pueden derivar las sales incluyen, por ejemplo, aminas primarias, secundarias, y terciarias, aminas sustituidas incluyendo aminas sustituidas que se presentan naturalmente, aminas cíclicas, resinas básicas de intercambio de iones, y similares, específicamente tales como isopropil-amina, trimetil-amina, dietil-amina, trietil-amina, tripropil-amina, y etanolamina. Las sales farmacéuticamente aceptables de la presente invención se pueden sintetizar a partir de un compuesto progenitor, una fracción básica o ácida, mediante los métodos químicos convencionales. En términos generales, estas sales se pueden preparar mediante la reacción de las formas del ácido libre de estos compuestos con una cantidad estequiométrica de la base apropiada

(tal como hidróxido, carbonato, bicarbonato, de Na, Ca, Mg, o K, o similares), o mediante la reacción de las formas de base libre de estos compuestos con una cantidad estequiométrica del ácido apropiado. Estas reacciones típicamente se llevan a cabo en agua o en un solvente orgánico, o en una mezcla de los dos. En términos generales, se prefieren los medios no acuosos como éter, acetato de etilo, etanol, isopropanol, o acetonitrilo, cuando sea practicable. Las listas de las sales adecuadas adicionales se pueden encontrar, por ejemplo, en "Remington's Pharmaceutical Sciences", 20ª Edición, Mack Publishing Company, Easton, Pa. (1985); y en "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" por Stahl y Wermuth (Wiley-VCH, Weinheim, Alemania, 2002).

Cualquier fórmula dada en la presente también pretende representar las formas no marcadas, así como las formas isotópicamente marcadas de los compuestos. Por ejemplo, cualquier hidrógeno representado por "H" en cualquiera de las fórmulas de la presente, pretende representar todas las formas isotópicas de hidrógeno (por ejemplo, ^{1}H, ^{2}H o D, ^{3}H); cualquier átomo de carbono representado por "C" en cualquiera de las fórmulas de la presente, pretende representar todas las formas isotópicas de carbono (por ejemplo, ^{11}C, ^{13}C, ^{14}C); cualquier nitrógeno representado por "N" pretende representar todas las formas isotópicas de nitrógeno (por ejemplo, ^{14}N, ^{15}N). Otros ejemplos de isótopos que se incluyen en la invención incluyen los isótopos de oxígeno, azufre, fósforo, flúor, yodo y cloro, tales como ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I. La invención

incluye diferentes compuestos isotópicamente marcados como se definen en la presente, por ejemplo aquéllos en donde están presentes isótopos radioactivos, tales como ^{3}H, ^{13}C, y ^{14}C. En una modalidad, los átomos en las fórmulas de la presente se presentan en su abundancia natural. En otra modalidad, uno o más átomos de hidrógeno pueden estar enriquecidos en ^{2}H; y/o uno o más átomos de carbono pueden estar enriquecidos en ^{11}C, ^{13}C o ^{14}C; y/o uno o más átomos de nitrógeno pueden estar enriquecidos en ^{14}N. Estos compuestos isotópicamente marcados son útiles en los estudios metabólicos (con ^{14}C), en los estudios de cinética de reacción (con, por ejemplo ^{2}H ó ^{3}H), en las técnicas de detección o de formación de imágenes, tales como tomografía por emisión de positrones (PET) o tomografía computarizada con emisión de un solo fotón (SPECT), incluyendo los ensayos de distribución del fármaco o del sustrato en el tejido, o en el tratamiento radioactivo de los pacientes. En particular, un ^{18}F o un compuesto marcado puede ser en particular deseable para los estudios de PET o SPECT. Los compuestos isotópicamente marcados de esta invención y los pro-fármacos de los mismos, se pueden preparar en términos generales llevando a cabo los procedimientos que se dan a conocer en los esquemas o en los Ejemplos y preparaciones que se describen más adelante, mediante la utilización de un reactivo isotópicamente marcado fácilmente disponible para sustituir a un reactivo no isotópicamente marcado.

Además, el enriquecimiento con isótopos más pesados, en particular deuterio (es decir, ^{2}H o D) puede proporcionar ciertas

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ventajas terapéuticas resultantes de la mayor estabilidad metabólica, por ejemplo un aumento de la vida media *in vivo* o requerimientos de dosificación reducida o una mejora en el índice terapéutico. Se entiende que el deuterio en este contexto se considera como un sustituyente de un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC. La concentración de este isótopo más pesado, específicamente deuterio, se puede definir por el factor de enriquecimiento isotópico. El término "factor de enriquecimiento isotópico", como se utiliza en la presente, significa la proporción entre la abundancia isotópica y la abundancia natural de un isótopo especificado. Si un sustituyente en un compuesto de esta invención es denotado como deuterio, este compuesto tiene un factor de enriquecimiento isotópico para cada átomo de deuterio designado de cuando menos 3500 (52.5 por ciento de incorporación de deuterio en cada átomo de deuterio designado), cuando menos 4000 (60 por ciento de incorporación de deuterio), cuando menos 4500 (67.5 por ciento de incorporación de deuterio), cuando menos 5000 (75 por ciento de incorporación de deuterio), cuando menos 5500 (82.5 por ciento de incorporación de deuterio), cuando menos 6000 (90 por ciento de incorporación de deuterio), cuando menos 6333.3 (95 por ciento de incorporación de deuterio), cuando menos 6466.7 (97 por ciento de incorporación de deuterio), cuando menos 6600 (99 por ciento de incorporación de deuterio), o cuando menos 6633.3 (99.5 por ciento de incorporación de deuterio).

Los compuestos isotópicamente enriquecidos de las fórmulas I'

o I a VIIC, se pueden preparar en términos generales, mediante técnicas convencionales conocidas para los expertos en este campo o mediante procesos análogos a aquéllos descritos en los ejemplos y preparaciones acompañantes, utilizando un reactivo isotópicamente enriquecido apropiado en lugar del reactivo no enriquecido previamente empleado.

Los solvatos farmacéuticamente aceptables de acuerdo con la invención incluyen aquéllos en donde el solvente de cristalización puede estar isotópicamente sustituido, por ejemplo, D_2O, d_6-acetona, d_6-DMSO.

Los compuestos de la invención, es decir, los compuestos de acuerdo con cualquiera de las fórmulas I' y I a VIIC, que contienen grupos capaces de actuar como donadores y/o aceptores para los enlaces de hidrógeno, pueden ser capaces de formar co-cristales con formadores de co-cristales adecuados. Estos co-cristales se pueden preparar a partir de los compuestos de acuerdo con cualquiera de las fórmulas I' y I a VIIC, mediante los procedimientos de formación de co-cristales conocidos. Estos procedimientos incluyen molienda, calentamiento, co-sublimación, co-fusión, o contacto en solución de los compuestos de acuerdo con cualquiera de las fórmulas I' y I a VIIC con el formador de co-cristales, bajo condiciones de cristalización, y el aislamiento de los co-cristales formados de esta manera. Los formadores de co-cristales adecuados incluyen aquéllos descritos en la Publicación Internacional Número WO 2004/078163. Por consiguiente, la invención proporciona además co-cristales, los

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cuales comprenden un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC.

Como se utiliza en la presente, el término "vehículo farmacéuticamente aceptable" incluye cualquiera y todos los solventes, medios de dispersión, recubrimientos, tensoactivos, antioxidantes, conservadores (por ejemplo, agentes antibacterianos, agentes antifúngicos), agentes isotónicos, agentes retardantes de absorción, sales, conservadores, fármacos, estabilizantes de fármacos, aglutinantes, excipientes, agentes de desintegración, lubricantes, agentes edulcorantes, agentes saborizantes, tintes, materiales similares, y combinaciones de los mismos, como serían conocidos por un experto ordinario en este campo (véase, por ejemplo, Remington's Pharmaceutical Sciences, 18ª Edición, Mack Printing Company, 1990, páginas 1289-1329). Excepto hasta donde cualquier vehículo convencional sea incompatible con el ingrediente activo, se contempla su uso en las composiciones terapéuticas o farmacéuticas.

El término "una cantidad terapéuticamente efectiva" de un compuesto de la presente invención se refiere a una cantidad del compuesto de la presente invención que provocará la respuesta biológica o médica de un sujeto, por ejemplo, la reducción o inhibición de la actividad de una enzima o de una proteína, o la mitigación de los síntomas, el alivio de las condiciones, el alentamiento o la demora del progreso de la enfermedad, o la prevención de una enfermedad, etc. En una modalidad no limitante,

el término "una cantidad terapéuticamente efectiva" se refiere a la cantidad del compuesto de la presente invención que, cuando se administra a un sujeto, es efectiva para: (1) cuando menos parcialmente aliviar, inhibir, prevenir y/o mitigar una condición, o un trastorno o una enfermedad (i) mediada por la endopeptidasa neutra EC 3.4. 24.11, o (ii) asociada con la actividad de la endopeptidasa neutra EC 3.4. 24.11, o (iii) caracterizada por una actividad anormal de la endopeptidasa neutra EC 3.4. 24.11; o (2) reducir o inhibir la actividad de la endopeptidasa neutra EC 3.4. 24.11; o (3) reducir o inhibir la expresión de la endopeptidasa neutra EC 3.4. 24.11. En otra modalidad no limitante, el término "una cantidad terapéuticamente efectiva" se refiere a la cantidad del compuesto de la presente invención que, cuando se administra a una célula, o a un tejido, o a un material biológico no celular, o a un medio, es efectiva para reducir o inhibir cuando menos parcialmente la actividad de la endopeptidasa neutra EC 3.4. 24.11; o para reducir o inhibir cuando menos parcialmente la expresión de la endopeptidasa neutra EC 3.4. 24.11.

Como se utiliza en la presente, el término "sujeto" se refiere a un animal. De preferencia, el animal es un mamífero. Un sujeto también se refiere, por ejemplo, a primates (por ejemplo, seres humanos), reses, ovejas, cabras, caballos, perros, gatos, conejos, ratas, ratones, peces, aves, y similares. En una modalidad preferida, el sujeto es un ser humano.

Como se utiliza en la presente, el término "inhibición" o

"inhibir" se refiere a la reducción o supresión de una condición, síntoma, o trastorno o enfermedad dados, o a una disminución significativa en la actividad de la línea base de una actividad o proceso biológico.

Como se utiliza en la presente, el término "tratar" o "tratamiento" de cualquier enfermedad o trastorno, se refiere, en una modalidad, a disminuir la enfermedad o el trastorno (es decir, hacer más lento o detener o reducir el desarrollo de la enfermedad o cuando menos uno de los síntomas clínicos de la misma). En otra modalidad, "tratar" o "tratamiento" se refiere a aliviar o mitigar cuando menos un parámetro físico, incluyendo aquéllos que puedan no ser discernibles por el paciente. En todavía otra modalidad, "tratar" o "tratamiento" se refiere a modular la enfermedad o el trastorno, ya sea físicamente (por ejemplo, la estabilización de un síntoma discernible), fisiológicamente (por ejemplo, la estabilización de un parámetro físico), o ambos. En todavía otra modalidad, "tratar" o "tratamiento" se refiere a prevenir o demorar el establecimiento o desarrollo o progreso de la enfermedad o del trastorno.

Como se utilizan en la presente, los términos "un," "uno," "el" y términos similares utilizados en el contexto de la presente invención (en especial en el contexto de las reivindicaciones) se deben interpretar para cubrir tanto el singular como el plural, a menos que se indique de otra manera en la presente o que sea claramente contradicho por el contexto.

El término "hipertensión" se refiere a una condición en donde la

presión sanguínea dentro de los vasos sanguíneos es más alta que lo normal a medida que circula a través del cuerpo. Cuando la presión sistólica excede de 150 mmHg o la presión diastólica excede de 90 mmHg durante un periodo de tiempo sostenido, se hace daño al cuerpo. Por ejemplo, una presión sistólica excesiva puede romper los vasos sanguíneos de cualquier parte, y cuando esto ocurre dentro del cerebro, da como resultado una embolia. La hipertensión también puede provocar engrosamiento y estrechamiento de los vasos sanguíneos, lo cual, por último, podría conducir a ateroesclerosis.

El término "diabetes tipo 2", incluyendo diabetes tipo 2 asociada con hipertensión, se refiere a una enfermedad en donde el páncreas no secreta suficiente insulina debido a un deterioro de la función de las células-beta pancreáticas, y/o en donde se presenta insensibilidad a la insulina producida (resistencia a la insulina). Típicamente, la glucosa en plasma en ayunas es de menos de 126 miligramos/decilitro, mientras que la pre-diabetes es, por ejemplo, una condición que se caracteriza por una de las siguientes condiciones: glucosa en ayunas deteriorada (110-125 miligramos/decilitro), y tolerancia deteriorada a la glucosa (niveles de glucosa en ayunas menores de 126 miligramos/decilitro, y nivel de glucosa post-prandial de entre 140 miligramos/decilitro y 199 miligramos/decilitro). La diabetes mellitus tipo 2 puede estar asociada con o sin hipertensión. La diabetes mellitus se presenta con frecuencia, por ejemplo, en las personas afroamericanas, latino-

/hispano-americanas, americanas nativas, asiático-americanas, y de las islas del Pacífico. Los marcadores de resistencia a la insulina incluyen HbA1C, HOMA IR, medición de fragmentos de colágeno, TGF-ß en la orina, PAI-1, y pro-renina.

Todos los métodos descritos en la presente se pueden llevar a cabo en cualquier orden adecuado, a menos que sea indicado de otra manera en la presente, o que sea claramente contradicho de otra manera por el contexto. El uso de cualquiera y todos los ejemplos, o de lenguaje (de ejemplo, "tal como") proporcionado en la presente, pretende meramente iluminar mejor la invención, y no presenta una limitación sobre el alcance de la invención reivindicada de otra manera.

Los compuestos de la presente invención se obtienen en la forma libre, como una sal de los mismos, o bien como derivados de pro-fármaco de los mismos.

Cuando están presentes tanto un grupo básico como un grupo ácido en la misma molécula, los compuestos de la presente invención también pueden formar sales internas, por ejemplo, moléculas zwiteriónicas.

La presente invención también proporciona pro-fármacos de los compuestos de la presente invención, que se convierten *in vivo* hasta los compuestos de la presente invención. Un pro-fármaco es un compuesto activo o inactivo que se modifica químicamente a través de la acción fisiológica *in vivo*, tal como hidrólisis, el metabolismo, y similares, en un compuesto de esta invención en seguida de la

administración del pro-fármaco a un sujeto. La idoneidad y las técnicas involucradas en la elaboración y utilización de pro-fármacos son bien conocidas por los expertos en la materia. Los pro-fármacos se pueden dividir conceptualmente en dos categorías no exclusivas: pro-fármacos bioprecursores y pro-fármacos portadores. Véase *The Practice of Medicinal Chemistry*, Capítulos 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001). En general, los pro-fármacos bioprecursores son compuestos que son inactivos o que tienen una baja actividad, comparándose con el compuesto de fármaco activo correspondiente, que contienen uno o más grupos protectores, y se convierten hasta la forma activa mediante el metabolismo o solvólisis. Tanto la forma del fármaco activo como cualesquiera productos metabólicos liberados deben tener una toxicidad aceptablemente baja.

Los pro-fármacos portadores son compuestos de fármaco que contienen una fracción de transporte, por ejemplo que mejoran la absorción y/o el suministro localizado a los sitios de acción. Deseablemente, para este pro-fármaco portador, el enlace entre la fracción de fármaco y la fracción de transporte es un enlace covalente, el pro-fármaco es inactivo o menos activo que el compuesto de fármaco, y cualquier fracción de transporte liberada es aceptablemente no tóxica. Para los pro-fármacos en donde la fracción de transporte se pretenda para mejorar la absorción, típicamente la liberación de la fracción de transporte debe ser rápida. En otros casos, es deseable utilizar una fracción que

proporcione una liberación lenta, por ejemplo ciertos polímeros u otras fracciones, tales como ciclodextrinas. Los pro-fármacos portadores, por ejemplo, se pueden utilizar para mejorar una o más de las siguientes propiedades: mayor lipofilicidad, mayor duración de los efectos farmacológicos, mayor especificidad del sitio, menor toxicidad y reacciones adversas, y/o mejora en la formulación del fármaco (por ejemplo, estabilidad, solubilidad en agua, supresión de una propiedad organoléptica o fisicoquímica indeseable). Por ejemplo, se puede aumentar la lipofilicidad mediante la esterificación de: (a) los grupos hidroxilo con ácidos carboxílicos lipofílicos (por ejemplo, un ácido carboxílico que tenga cuando menos una fracción lipofílica), o (b) los grupos de ácido carboxílico con alcoholes lipofílicos (por ejemplo, un alcohol que tenga cuando menos una fracción lipofílica, por ejemplo, alcoholes alifáticos).

Los pro-fármacos de ejemplo son, por ejemplo, los ésteres de ácidos carboxílicos y los derivados S-acílicos de tioles y los derivados O-acílicos de alcoholes o fenoles, en donde el acilo tiene el significado como se define en la presente. Se prefieren los derivados de éster farmacéuticamente aceptables que se pueden convertir mediante solvólisis bajo condiciones fisiológicas hasta el ácido carboxílico progenitor, por ejemplo los ésteres de alquilo inferior, ésteres de cicloalquilo, ésteres de alquenilo inferior, ésteres de bencilo, ésteres de alquilo inferior mono- o di-sustituidos, tales como los ésteres de ω-(amino, mono- o di-alquilo inferior-amino, carboxilo, alcoxilo inferior-carbonilo)-alquilo inferior, los ésteres de

α-(alcanoiloxilo inferior, alcoxilo inferior-carbonilo, o di-alquilo inferior-amino-carbonilo)-alquilo inferior, tales como el pivaloiloxi-metil-éster y similares, convencionalmente utilizados en la técnica. En adición, las aminas se han enmascarado como derivados sustituidos por aril-carboniloxi-metilo que se disocian mediante las esterasas *in vivo*, liberando el fármaco libre y formaldehído (Bundgaard, *J. Med. Chem.* 2503 (1989)). Más aún, los fármacos que contienen un grupo NH ácido, tal como imidazol, imida, indol, y similares, se han enmascarado con grupos N-aciloxi-metilo (Bundgaard, *Design of Prodrugs*, Elsevier (1985)). Los grupos hidroxilo se han enmascarado como ésteres y éteres. La Patente Europea Número EP 039,051 (Sloan y Little) da a conocer pro-fármacos de ácido hidroxámico de base de Mannich, su preparación, y su uso.

Adicionalmente, los compuestos de la presente invención, incluyendo sus sales, también se pueden obtener en la forma de sus hidratos, o pueden incluir otros solventes utilizados para su cristalización.

ASPECTOS SINTÉTICOS GENERALES

Los compuestos de la invención se pueden sintetizar empleando los métodos descritos en los siguientes esquemas, ejemplos, y utilizando las técnicas reconocidas en este campo. Todos los compuestos descritos en la presente se incluyen en la invención como compuestos. Los compuestos de la invención se pueden sintetizar de acuerdo con cuando menos uno de los métodos

descritos en los Esquemas 1 a 4.

Dentro del alcance de este texto, solamente un grupo fácilmente removible que no sea un constituyente del producto final deseado particular de los compuestos de la presente invención se designa como un "grupo protector", a menos que el contexto lo indique de otra manera. La protección de los grupos funcionales mediante estos grupos protectores, los grupos protectores mismos, y sus reacciones de disociación se describen, por ejemplo, en los trabajos de referencia convencionales, tales como J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, Londres y Nueva York 1973, en T. W. Greene y P. G. M. Wuts, "Protective Groups in Organic Synthesis", Tercera Edición, Wiley, Nueva York 1999.

Las sales de los compuestos de la presente invención que tengan cuando menos un grupo formador de sal, se pueden preparar de una manera conocida por sí misma. Por ejemplo, las sales de los compuestos de la presente invención que tengan grupos ácidos se pueden formar, por ejemplo, mediante el tratamiento de los compuestos con compuestos de metales, tales como sales de metales alcalinos de los ácidos carboxílicos orgánicos adecuados, por ejemplo la sal sódica del ácido 2-etil-hexanoico, con compuestos de metales alcalinos o de metales alcalinotérreos orgánicos, tales como los hidróxidos, carbonatos, o carbonatos ácidos correspondientes, tales como hidróxido, carbonato, o carbonato ácido de sodio o de potasio, con los compuestos de calcio

correspondientes, o con amoniaco o una amina orgánica adecuada, utilizándose de preferencia cantidades estequiométricas o solamente un pequeño exceso del agente formador de sal. Las sales de adición de ácido de los compuestos de la presente invención se obtienen de la manera acostumbrada, por ejemplo mediante el tratamiento de los compuestos con un ácido o con un reactivo de intercambio de aniones adecuado. Se pueden formar las sales internas de los compuestos de la presente invención que contengan grupos formadores de sales ácidos y básicos, por ejemplo un grupo carboxilo libre y un grupo amino libre, por ejemplo, mediante la neutralización de las sales, tales como las sales de adición de ácido, hasta el punto isoeléctrico, por ejemplo con bases débiles, o mediante su tratamiento con intercambiadores de iones.

Las sales se pueden convertir de la manera acostumbrada en los compuestos libres; las sales de metales y de amonio se pueden convertir, por ejemplo, mediante su tratamiento con ácidos adecuados, y las sales de adición de ácido, por ejemplo, mediante su tratamiento con un agente básico adecuado.

Las mezclas de isómeros que se pueden obtener de acuerdo con la invención se pueden separar de una manera conocida por sí misma en los isómeros individuales; los diaestereoisómeros se pueden separar, por ejemplo, mediante división entre mezclas de solventes polifásicas, recristalización, y/o separación cromatográfica, por ejemplo sobre gel de sílice, o, por ejemplo, mediante cromatografía de líquidos a presión media sobre una columna de

fase inversa, y los racematos se pueden separar, por ejemplo, mediante la formación de sales con reactivos formadores de sales ópticamente puros y la separación de la mezcla de diaestereoisómeros que se puede obtener de esta manera, por ejemplo por medio de cristalización fraccionaria, o mediante cromatografía sobre materiales de columna ópticamente activos.

Los intermediarios y los productos finales se pueden procesar y/o purificar de acuerdo con los métodos convencionales, por ejemplo empleando métodos cromatográficos, métodos de distribución, (re-)cristalización, y similares.

Lo siguiente se aplica en general a todos los procesos mencionados anteriormente en la presente y más adelante en la presente.

Todos los pasos del proceso mencionados anteriormente se pueden llevar a cabo bajo condiciones de reacción que son conocidas por sí mismas, incluyendo las mencionadas de una manera específica, en ausencia, o por costumbre en la presencia de solventes o diluyentes, incluyendo, por ejemplo, los solventes o diluyentes que sean inertes hacia los reactivos utilizados y los disuelvan, en ausencia o en la presencia de catalizadores, agentes de condensación o neutralizantes, por ejemplo intercambiadores de iones, tales como intercambiadores de cationes, por ejemplo en la forma de H^+, dependiendo de la naturaleza de la reacción, y/o de los reactivos, a temperatura reducida, normal, o elevada, por ejemplo en un intervalo de temperatura de aproximadamente -100°C a

aproximadamente 190°C, incluyendo, por ejemplo, de aproximadamente -80°C a aproximadamente 150°C, por ejemplo de -80°C a -60°C, a temperatura ambiente, de -20°C a 40°C, o a la temperatura de reflujo, bajo presión atmosférica o en un recipiente cerrado, donde sea apropiado bajo presión, y/o en una atmósfera inerte, por ejemplo bajo una atmósfera de argón o de nitrógeno.

En todas las etapas de las reacciones, las mezclas de isómeros que se formen se pueden separar en los isómeros individuales, por ejemplo diaestereoisómeros o enantiómeros, o en cualesquiera mezclas de isómeros deseadas, por ejemplo racematos, o mezclas de diaestereoisómeros, por ejemplo, de una manera análoga a los métodos descritos bajo los "Pasos adicionales del proceso".

Los solventes a partir de los cuales se pueden seleccionar los solventes que son adecuados para cualquier reacción particular incluyen los mencionados de una manera específica, o, por ejemplo, agua, ésteres, tales como alcanoatos inferiores de alquilo inferior, por ejemplo acetato de etilo, éteres, tales como éteres alifáticos, por ejemplo dietil-éter, o éteres cíclicos, por ejemplo tetrahidrofurano o dioxano, hidrocarburos aromáticos líquidos, tales como benceno o tolueno, alcoholes, tales como metanol, etanol, o 1- ó 2-propanol, nitrilos, tales como acetonitrilo, hidrocarburos halogenados, tales como cloruro de metileno o cloroformo, amidas de ácido, tales como dimetil-formamida o dimetil-acetamida, bases, tales como bases de nitrógeno heterocíclico, por ejemplo piridina ó N-metil-pirrolidin-2-

ona, anhídridos de ácido carboxílico, tales como anhídridos de ácido alcanoico inferior, por ejemplo anhídrido acético, hidrocarburos cíclicos, lineales o ramificados, tales como ciclohexano, hexano, o isopentano, metil-ciclohexano, o mezclas de estos solventes, por ejemplo soluciones acuosas, a menos que se indique de otra manera en la descripción de los procesos. Estas mezclas de solventes también se pueden utilizar en el procesamiento, por ejemplo mediante cromatografía o división.

Los compuestos, incluyendo sus sales, también se pueden obtener en la forma de hidratos, o, por ejemplo, sus cristales pueden incluir al solvente utilizado para la cristalización. Puede haber diferentes formas cristalinas presentes.

La invención se refiere también a las formas del proceso en donde un compuesto que se pueda obtener como un intermediario en cualquier etapa del proceso, se utiliza como material de partida, y se llevan a cabo los pasos restantes del proceso, o en donde se forma un material de partida bajo las condiciones de reacción, o se utiliza en la forma de un derivado, por ejemplo en una forma protegida o en la forma de una sal, o un compuesto que se pueda obtener mediante el proceso de acuerdo con la invención se produce bajo las condiciones del proceso, y se procesa adicionalmente *in situ*.

Todos los materiales de partida, bloques de construcción, reactivos, ácidos, bases, agentes deshidratantes, solventes, y catalizadores utilizados para la síntesis de los compuestos de la presente invención, están comercialmente disponibles, o se pueden

producir mediante los métodos de síntesis orgánica conocidos por un experto ordinario en este campo (Houben-Weyl, 4ª Edición, 1952, Methods of Organic Synthesis, Thieme, Volumen 21).

Los compuestos de la invención de acuerdo con cualquiera de las fórmulas I' y I a VIIC, se pueden preparar mediante el procedimiento descrito en las siguientes secciones.

Abreviaturas:

ATP: 5'-trifosfato de adenosina	AS: Sintasa de aldosterona
Alloc: aliloxi-carbonilo	BOC: terbutil-carboxilo
BOP: hexafluorofosfato de benzotriazol-1-iloxi)-tris-(dimetil-amino)-fosfonio	BINAP: 2,2'-bis-(difenil-fosfino)-1,1'-binaftilo racémico
br: amplia	bs: amplia singulete
Ac: acetilo	Atm: atmósfera
Aq: acuoso	calcd: calculado
Bn: bencilo	Cbz: benciloxi-carbonilo
Bu, i-bu y t-Bu: butilo, isobutilo y terbutilo	Pr e i-Pr: propilo e isopropilo
CDI: 1,1'-carbonil-di-imidazol	COD: 1,5-ciclo-octadieno
DBU: 1,8-diazabiciclo-[5.4.0]-	DCC: 1,3-diciclohexil-carbodi-

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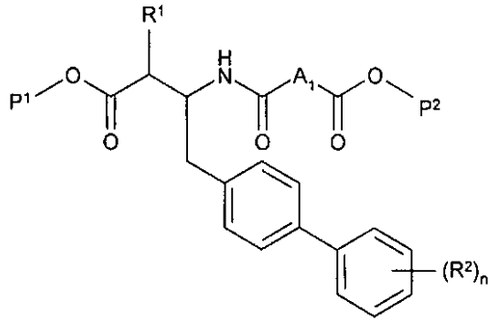
undec-7-eno	imida
DIAD: azodicarboxilato de di-isopropilo	DAST: trifluoruro de (dietil-amino)-azufre
d: doblete dd: doblete de dobletes	DCM: dicloro-metano
DIEA: dietil-isopropil-amina	DME: 1,4-dimetoxi-etano
DMF: *N*,*N*-dimetil-formamida	DMSO: sulfóxido de dimetilo
DIPEA: N,N-di-isopropil-etil-amina	DMAP: N,N-dimetil-amino-piridina
Dppb: 1,2-bis-(difenil-fosfino)-butano	Dppe: 1,2-bis-(difenil-fosfino)-etano
DAD: detector de arreglo de diodos	DTT: ditioeritritol
DPPA: difenil-fosforil-azida	EDCI, EDIC: clorhidrato de N-etil-N'-(3-dimetil-amino-propil)-carbodi-imida
EDTA: ácido etilen-diamina-tetra-acético	ESI: ionización por electroaspersión
Et y EtOAc: etilo y acetato de	EDC: clorhidrato de N-etil-N'-(3-

etilo	dimetil-amino-propil)-carbodi-imida
HATU: hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametil-uronio	HOBt: 1-hidroxi-7-azabenzotriazol
HPLC: cromatografía de líquidos a alta presión	LC y LCMS: cromatografía de líquidos y cromatografía de líquidos con espectrometría de masas
H: hora(s)	HOAt: 1-hidroxi-7-azabenzotriazol
IR: infrarrojo	LDA: di-isopropil-amida de litio
KHMDS: bis-(trimetil-silil)-amida de potasio	LHMDS: bis-(trimetil-silil)-amida de litio
LTA: tetra-acetato de plomo	NHMDS: bis-(trimetil-silil)-amida de sodio
MeOD: metanol-d4	MeOH: metanol
MS: espectrometría de masas	m: multiplete
min: minutos	m/z: proporción de la masa a la carga

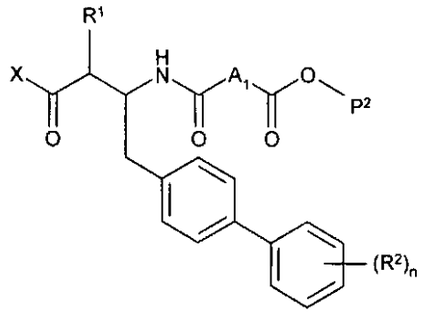
Ms: mesilo	Me: metilo
M y mM: Molar y milimolar	Mg: miligramos
n.d.: no determinado	NMR: resonancia magnética nuclear
ppm: partes por millón	Pr e iPr: propilo e isopropilo
Ph: fenilo	Pd/C: paladio sobre carbón
PyBOP: hexafluorofosfato de benzotriazol-1-il-oxi-tripirrolidino-fosfonio	RT: temperatura ambiente
PIDA: bis-(trifluoro-acetato) de yodo-benceno	PIFA: diacetato de yodo-benceno
PS: soportado por polímero	RP: fase inversa
s: singulete y t: triplete	Ts: tosilo
TFA: ácido trifluoro-acético	THF: tetrahidrofurano
Tf: triflato	tBu: terbutilo
TLC: cromatografía de capa delgada	Tris·HCl: clorhidrato de amino-tris-(hidroxi-metil)-metano
µL, mL, y L: microlitros, mililitros y litros	TMS: trimetil-sililo

WSC: carbodi-imida (N-etil-N'-(3-dimetil-amino-propil)-carbodi-imida soluble en agua	UV: ultravioleta

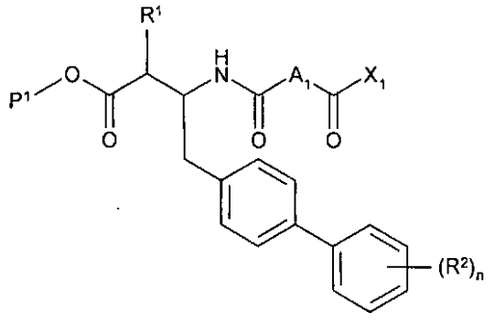
Los compuestos de la invención de la fórmula II se pueden preparar mediante la hidrólisis de los intermediarios **A** a **C**, en donde X, X^1, A^1, R^1, R^2 y n tienen la definición de la fórmula I o I' anteriores; y P^1 y P^2 son los grupos protectores apropiados seleccionados a partir de, pero no limitándose a, metilo, etilo, isopropilo, butilo terciario, metoxi-bencilo o bencilo.



Intermediario A

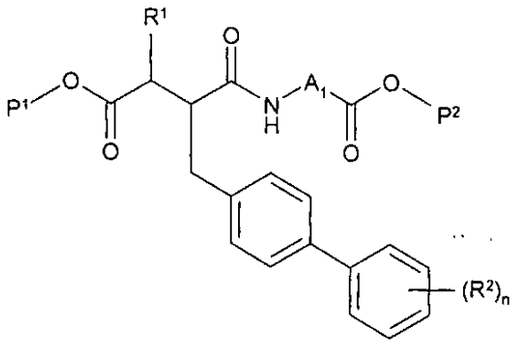


Intermediario B

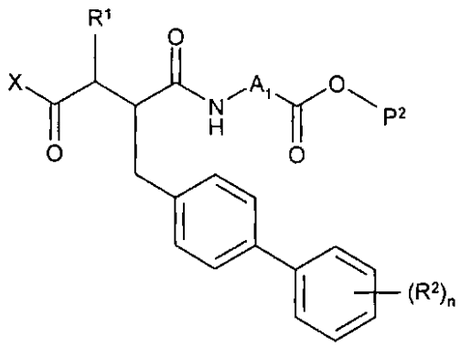


Intermediario C

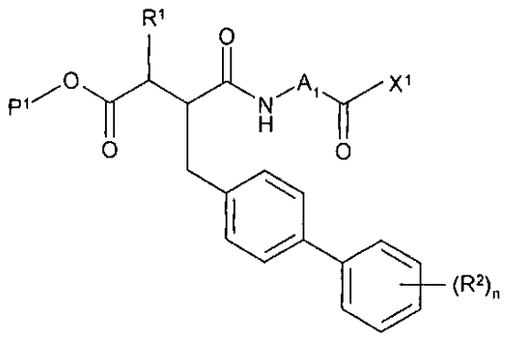
Los compuestos de la invención de la fórmula III se pueden preparar mediante la hidrólisis de los intermediarios **D**, **E** o **F**, en donde X, X^1, A^1, R^1, R^2 y n tienen la definición de la fórmula I o I' anteriores; y P^1 y P^2 pueden ser los grupos protectores apropiados seleccionados a partir de, pero no limitándose a, metilo, etilo, isopropilo, butilo terciario, metoxi-bencilo o bencilo.



Intermediario D



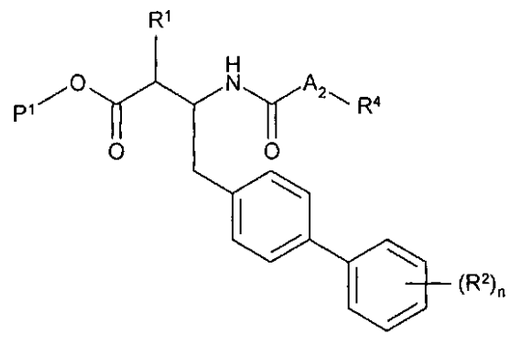
Intermediario E



Intermediario F

Los compuestos de la invención de la fórmula VII se pueden

preparar mediante la hidrólisis del intermediario **G**, en donde A^2, R^1, R^2, R^4 y n tienen la definición de la fórmula I o I' anteriores; y P^1 puede ser un grupo protector apropiado seleccionado a partir de, pero no limitándose a, metilo, etilo, isopropilo, butilo terciario, metoxi-bencilo o bencilo.



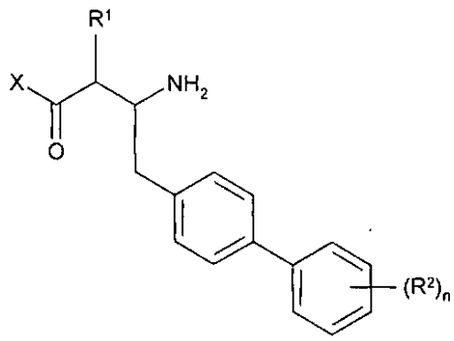
Intermediario G

Se pueden aplicar los métodos convencionales para la hidrólisis de los intermediarios A a G utilizando una base seleccionada a partir de, pero no limitándose a, NaOH, KOH o LiOH, o un ácido seleccionado a partir de, pero no limitándose a, ácido trifluoro-acético o HCl. Cuando P^1 o P^2 es bencilo o metoxi-bencilo, el método preferible de desprotección es la hidrogenación en la presencia de un catalizador, tal como, pero no limitándose a, paladio sobre carbón bajo hidrógeno.

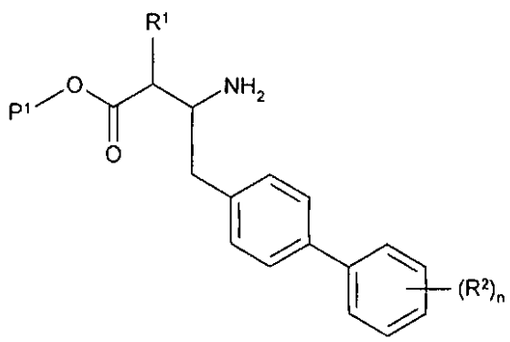
Los intermediarios **A**, **B**, **C** o **G** se pueden preparar empleando el siguiente proceso, el cual comprende: condensar un intermediario **H** o **I**, en donde X, P^1, R^1, R^2 y n son como se describen

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anteriormente:

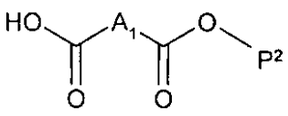


Intermediario H

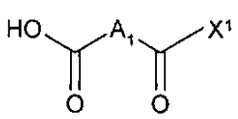


Intermediario I

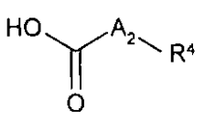
con un intermediario **J**, **K** o **L**, en donde X^1, A^1, A^2, R^4 y P^2 se describen anteriormente.



Intermediario J



Intermediario K

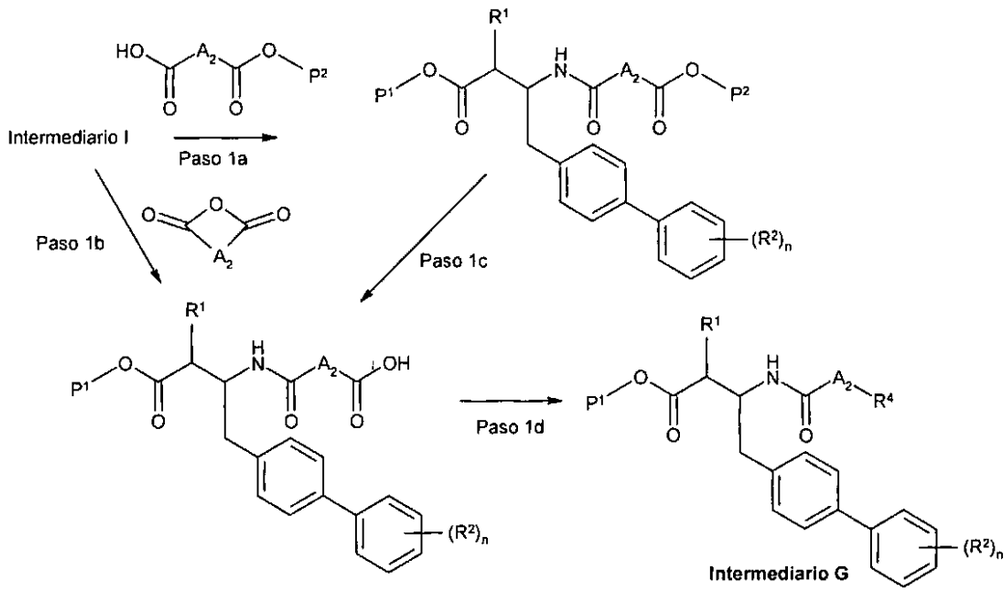


Intermediario L

Se pueden aplicar los métodos de condensación conocidos, incluyendo, pero no limitándose a, la conversión del intermediario **J**, **K** o **L** hasta su haluro de ácido correspondiente, utilizando reactivos tales como cloruro de tionilo o cloruro de oxalilo, o la conversión del intermediario **J**, **K** o **L** hasta el anhídrido mixto, utilizando reactivos tales como ClC(O)O-isobutilo o cloruro de 2,4,6-tricloro-benzoílo, seguida por la reacción del haluro de ácido o del anhídrido mixto con el Intermediario **H** o **I**, en la presencia o en ausencia de una base, tal

como amina terciaria (por ejemplo, trietil-amina, DIPEA, o *N*-metil-morfolina) o un derivado de piridina (por ejemplo, piridina, 4-(dimetil-amino)-piridina, ó 4-pirrolidino-piridina). De una manera alternativa, el intermediario **J**, **K**, o **L** se puede acoplar con H o I utilizando reactivos de acoplamiento, tales como DCC, EDCI, PyBOP o BOP en la presencia o en ausencia de un reactivo, tal como 1-hidroxi-benzotriazol, 1-hidroxi-7-aza-benzotriazol o pentafluoro-fenol.

El intermediario **G**, en donde R^4 es un tetrazol, se puede sintetizar de acuerdo con el esquema 1:



Esquema 1

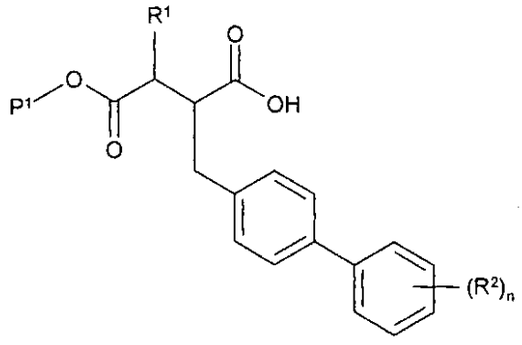
en donde A^2, R^1, R^2, R^4, P^1, P^2 y n are como se definen anteriormente.

En el paso 1a, el intermediario **I** se hace reaccionar con un ácido carboxílico apropiado, utilizando reactivos de acoplamiento

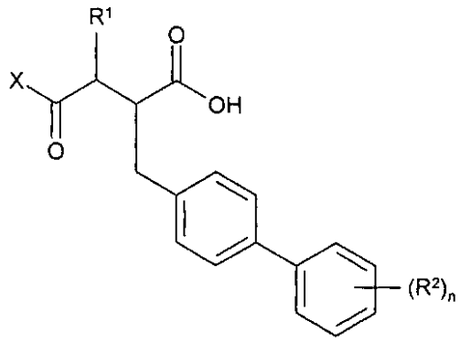
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convencionales seleccionados a partir de, pero no limitándose a, DCC, EDCI, PyBOP o BOP, en la presencia o en ausencia de un reactivo, tal como 1-hidroxi-benzotriazol, 1-hidroxi-7-azabenzotriazol o pentafluoro-fenol; seguido por la remoción del grupo protector P^2 en el paso 1c, utilizando una base seleccionada a partir de, pero no limitándose a, NaOH, KOH o LiOH, o un ácido seleccionado a partir de, pero no limitándose a, ácido trifluoro-acético o HCl, o hidrogenación con un catalizador, tal como, pero no limitándose a, paladio sobre carbón bajo hidrógeno. De una manera alternativa, el intermediario I se hace reaccionar con un anhídrido apropiado, en la presencia de una base seleccionada a partir de, pero no limitándose a, piridina, trietil-amina o di-isopropil-etil-amina (paso 1b); seguido por la conversión del ácido carboxílico en un tetrazol (paso 1b) empleando un método similar al que se describe en *Journal of Medicinal Chemistry* 1998, 41, 1513.

El intermediario **D**, **E** o **F** se puede preparar empleando el siguiente proceso, el cual comprende: condensar un intermediario **M**, en donde X, P^1, R^1, R^2 y n son como se definen anteriormente;

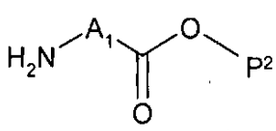


Intermediario M

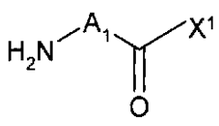


Intermediario N

con un intermediario **Q** o **S**, en donde X^1, A^1 y P^2 tienen el significado como se define anteriormente.



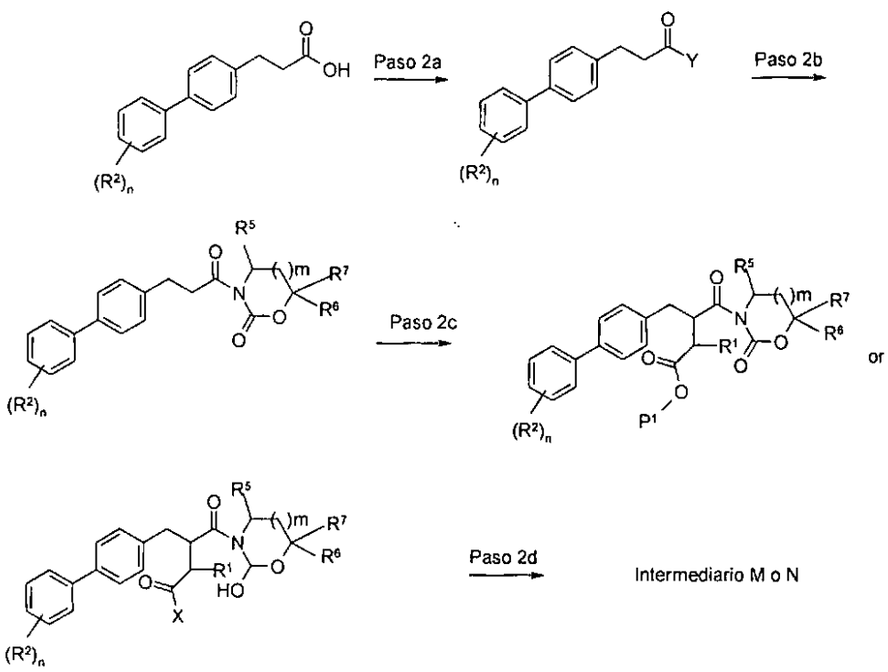
Intermediario Q



Intermediario S

Se pueden aplicar los métodos de condensación conocidos, incluyendo, pero no limitándose a, la conversión del intermediario **M** o **N** hasta un haluro de ácido, utilizando reactivos tales como cloruro de tionilo o cloruro de oxalilo, o la conversión del intermediario **M** o **N** hasta un anhídrido mixto, utilizando reactivos tales como ClC(O)O-isobutilo o cloruro de 2,4,6-tricloro-benzoílo, seguida por la reacción del cloruro de ácido o anhídrido mixto con el intermediario **Q** o **S**, en la presencia o en ausencia de una base, tal como amina terciaria (por ejemplo, trietil-amina, DIPEA, o *N*-metil-morfolina), o un derivado de piridina (por ejemplo, piridina, 4-(dimetil-amino)-piridina, ó 4-pirrolidino-piridina); De una manera alternativa, el intermediario M o N se puede acoplar con el intermediario **Q** o **S** utilizando un reactivo, tal como DCC, EDCI, PyBOP o BOP, en la presencia o en ausencia de un reactivo, tal como 1-hidroxi-benzotriazol, 1-hidroxi-7-azabenzotriazol o pentafluoro-fenol.

El intermediario **M** o **N** se puede preparar de acuerdo con los siguientes procedimientos generales descritos en el esquema 2:



Esquema 2

en donde R^1, R^2, X y n son como se definen anteriormente, y en donde m = 0 ó 1; P^1 es un grupo protector seleccionado a partir de, pero no limitándose a, hidrógeno, metilo, etilo, propilo, butilo terciario, metoxi-metilo, terbutil-dimetil-sililo, tetrahidro-furanilo, bencilo, alilo o fenilo; R^5 es, por ejemplo, hidrógeno, metilo, etilo, isopropilo, bencilo o fenilo; R^6 y R^7 son independientemente hidrógeno, metilo, etilo, isopropilo, bencilo o fenilo. y se selecciona a partir de, pero no limitándose a, cloro, bromo, yodo, benzotriazoloxilo, piridinio, *N,N*-dimetil-amino-piridinio, pentafluoro-fenoxilo, fenoxilo, 4-cloro-fenoxilo, $-OCO_2Me$, $-OCO_2Et$, terbutoxi-carbonilo o -OCC(O)O-isobutilo.

En el paso (2a), se pueden aplicar los métodos convencionales para preparar el haluro de ácido correspondiente, tal como el uso de

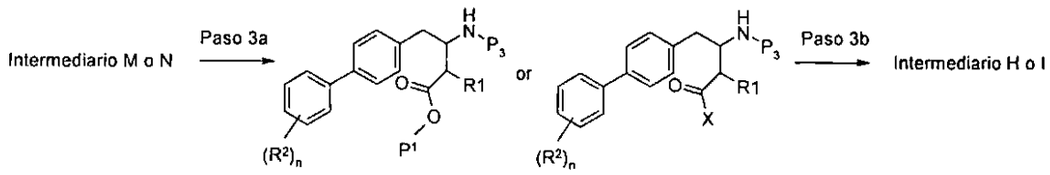
cloruro de tionilo, cloruro de oxalilo; o se pueden aplicar los métodos convencionales para preparar el anhídrido mixto o el catión de acil-piridinio, tales como el uso de cloruro de pivaloílo con una amina terciaria (por ejemplo, trietil-amina, DIPEA, *N*-metil-morfolina) en la presencia o en ausencia de un derivado de piridina (por ejemplo, piridina, 4-(dimetil-amino)-piridina, 4-pirrolidino-piridina), cloruro de 2,4,6-tricloro-benzoílo con una amina terciaria (por ejemplo, trietil-amina, DIPEA, *N*-metil-morfolina) en la presencia o en ausencia de un derivado de piridina (por ejemplo, piridina, 4-(dimetil-amino)-piridina, 4-pirrolidino-piridina), o ClC(O)O-*i*-Bu con una amina terciaria (por ejemplo, trietil-amina, DIPEA, *N*-metil-morfolina) en la presencia o en ausencia de un derivado de piridina (por ejemplo, piridina, 4-(dimetil-amino)-piridina, 4-pirrolidino-piridina); o se pueden aplicar los métodos convencionales para preparar el éster activado, tales como el uso de 1-hidroxi-benzotriazol, 1-hidroxi-7-azabenzotriazol o pentafluoro-fenol en la presencia de un reactivo de acoplamiento (por ejemplo, DCC, EDCI) o BOP.

En el paso (2b), se pueden emplear los métodos convencionales para preparar las *N*-acil-oxazolidinonas (m = 0). Los ejemplos ilustrativos de esta química se ilustran en *Aldrichchimica Acta* 1997, Volumen 30, páginas 3 – 12 y en las referencias citadas en el mismo; o se pueden emplear los métodos convencionales para preparar la *N*-aciloxazinanona (m = 1). Un ejemplo ilustrativo de esta química se ilustra en *Organic and Biomolecular Chemistry* 2006, Volumen 4, Número 14, páginas 2753 – 2768.

En el paso (2c), se pueden emplear los métodos convencionales para alquilación. Un ejemplo ilustrativo se ilustra en *Chemical Reviews* 1996, 96(2), 835 – 876, y en las referencias citadas en el mismo.

En el paso (2d), se pueden emplear los métodos convencionales para la disociación de *N*-acil-oxazolidinona o *N*-acil-oxazinanona. Los ejemplos ilustrativos de esta química se ilustran en *Aldrichchimica Acta* 1997, Volumen 30, páginas 3 – 12, y en las referencias citadas en el mismo.

El intermediario H o I se puede preparar de acuerdo con los siguientes procedimientos generales descritos en los Esquemas 3 y 4:



Esquema 3

en donde R^1, R^2, X y n son como se definen anteriormente, y en donde P^3 es un grupo protector seleccionado a partir de, pero no limitándose a, butilo terciario, bencilo, trifenil-fosfinilo, terbutoxi-carbonilo, benciloxi-carbonilo, aliloxi-carbonilo, acetilo, o trifluoro-acetilo.

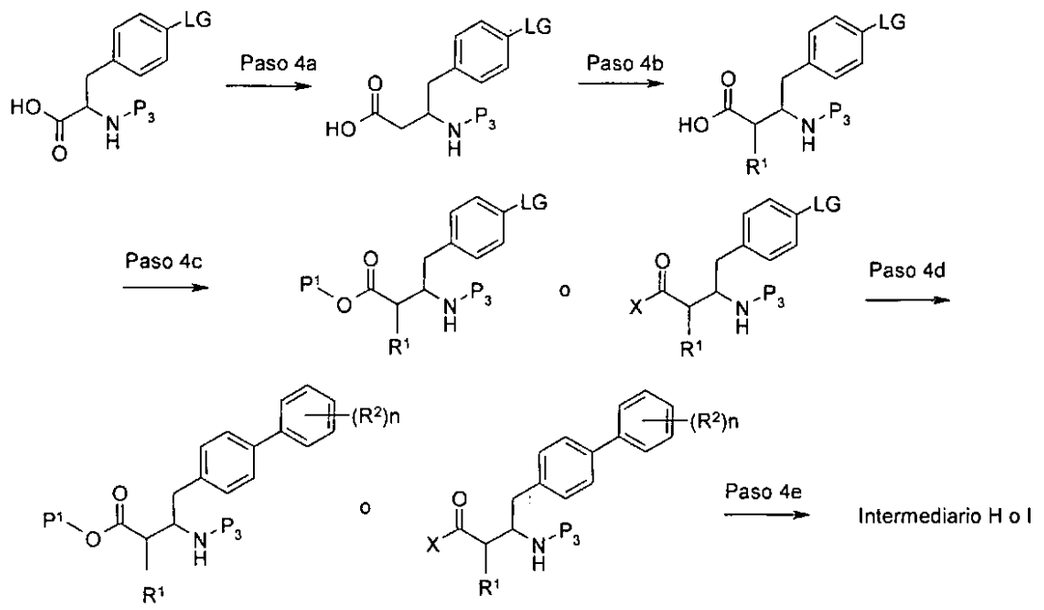
en el paso (3a), se pueden emplear los métodos convencionales para la introducción de la parte de amina, tal como utilizando: ya sea el tratamiento simultáneo con, o bien el tratamiento por pasos mediante, la formación de acil-azida

correspondiente, utilizando cloruro de tionilo (o $ClCO_2R^8$), NaN_3 (o $TMSN_3$), y R^9OH (en donde R^8 y R^9 son hidrógeno, metilo, etilo, butilo terciario, alilo, bencilo o 4-metoxi-bencilo); o ya sea el tratamiento simultáneo con, o bien el tratamiento por pasos mediante, la formación de acil-azida correspondiente, con DPPA y R^9OH (en donde R^9 se define como anteriormente); o se pueden emplear los métodos convencionales para la conversión hasta la carboxamida correspondiente, seguida por el tratamiento con el equivalente de NH_3 y ya sea el tratamiento simultáneo, o bien el tratamiento por pasos, con LTA o reactivos de yodo hipervalentes (por ejemplo, PIDA, PIFA, PhI(OH)OTs, PhIO), y R^9OH (en donde R^9 se define como anteriormente); o se pueden emplear los métodos convencionales para la conversión hasta la carboxamida correspondiente, y ya sea el tratamiento simultáneo, o bien el tratamiento por pasos, con BR^2 y MOH (en donde M se define en la presente, por ejemplo, Na, K, Ba o Ca); o se pueden emplear los métodos convencionales para la conversión hasta la carboxamida correspondiente, y el tratamiento con MOZ o $NaBrO_2$ (en donde Z se define en la presente, por ejemplo, Cl o Br); o se pueden emplear los métodos convencionales para la conversión hasta la carboxamida correspondiente, y el tratamiento con $Pb(OAc)_4$ y R^9OH (en donde R^9 se define como anteriormente); o se pueden emplear los métodos convencionales para la conversión hasta el ácido hidroxámico correspondiente, seguida por el tratamiento con H_2NOH o H_2NOTMS y el tratamiento con Ac_2O, Boc_2O, $R^{10}COCl$, $R^{10}SO_2Cl$, $R^{10}PO_2Cl$ (en

donde R^{10} se define en la presente, por ejemplo, Me, Et, tBu o fenilo), cloruro de tionilo, EDCI, DCC, o 1-cloro-2,4-dinitro-benceno, en la presencia o en ausencia de una base (por ejemplo, piridina, Na_2CO_3 acuoso, trietil-amina, DIPEA), y el tratamiento con R^9OH en la presencia de una base (por ejemplo, DBU, ZOH, DIPEA) (en donde R^9 y Z se definen como anteriormente).

En el paso (3b), se pueden aplicar los métodos convencionales para remover los grupos protectores P_3, tales como hidrólisis de base, utilizando NaOH, KOH, o LiOH, hidrólisis de ácido, utilizando ácido trifluoro-acético o HCl, o hidrogenación, utilizando paladio sobre carbón bajo hidrógeno.

El esquema 4 describe una síntesis alternativa del intermediario **H** o **I**:



Esquema 4

en donde LG es un grupo saliente seleccionado a partir de, pero no limitándose a, Cl, Br, I, OMs, OTs u OTf.

En el paso (4a), se pueden emplear los métodos convencionales para la homologación de Arndt-Eistert. Un ejemplo ilustrativo de esta química se ilustra en "Enantioselective Synthesis of ß-amino acids", Segunda Edición, John Wiley and Sons, Inc., NJ (2005), ya sea directamente o bien de una manera análoga.

En el paso (4b), se pueden emplear los métodos convencionales para alquilación, tales como utilizando R^1LG en la presencia de una base, tal como LDA, NHMDS, LHMDS o KHMDS.

En el paso (4c), se pueden emplear los métodos convencionales para proteger al ácido carboxílico, tales como utilizando $TMSCHN_2$ (para el metil-éster), P^1LG/base (por ejemplo, K_2CO_3, $NaHCO_3$, Cs_2CO_3 o K_3PO_4), cloruro de tionilo (o cloruro de oxalilo)/R^9OH, DCC(o EDCI)/DMAP/R^9OH, BOP/R^9OK (o R^9ONa), $(R^9O)_2CHNMe_2$, CDI/DBU/ R^9OH en donde R^9 tiene el mismo significado que el que se define anteriormente, o isobutileno/H_2SO_4 (para el terbutilo).

En el paso (4d), se pueden aplicar los métodos convencionales para la reacción de acoplamiento de Suzuki, tales como utilizando una especie paladio (o níquel) [por ejemplo, $Pd(PPh_3)_4$, $PdCl_2(dppf)$, $Pd(OAc)_2$/una fosfina (por ejemplo, PPh_3, dppf, PCy_3, $P(tBu)_3$, XPhos), Pd/C, $Pd_2(dba)_3$/una fosfina (por ejemplo, PPh_3, dppf, PCy_3, $P(tBu)_3$, XPhos), $Ni(COD)_2$/una fosfina (o dppe, dppb, PCy_3),

$Ni(dppf)Cl_2$], una base (por ejemplo, KF, CsF, K_3PO_4, Na_2CO_3, K_2CO_3, Cs_2CO_3, NaOH, KOH, NaO-*t*-Bu, KO-*t*-Bu), y (R^2)n-$PhB(OH)_2$ [o (R^2)n-$PhBF_3K$].

En el paso (4e), se pueden aplicar los métodos convencionales para remover los grupos protectores P_3, tales como hidrólisis de base utilizando NaOH, KOH, o LiOH, hidrólisis de ácido, utilizando ácido trifluoro-acético o HCl, o hidrogenación utilizando paladio sobre carbón bajo hidrógeno.

De una manera alternativa, el intermediario H o I se puede preparar siguiendo las rutas sintéticas ilustradas en *Tetrahedron Letters*, 2008, Volumen 49, Número 33, páginas 4977-4980, ya sea directamente o bien de una manera análoga, y se convierte el ácido borónico obtenido en un bifenilo sustituido mediante los métodos ilustrados en *Organic Letters*, 2002, Volumen 4, Número 22, páginas 3803 – 3805.

De una manera alternativa, el intermediario H o I se puede preparar siguiendo las rutas sintéticas ilustradas en *Tetrahedron: Asymetry*, 2006, Volumen 17, Número 2, páginas 205-209, ya sea directamente o bien de una manera análoga.

De una manera alternativa, el intermediario H o I se puede preparar mediante los métodos de la reacción de Mannich. Los ejemplos ilustrativos de esta química se ilustran en "Enantioselective Synthesis of ß-amino acids", Segunda Edición, John Wiley and Sons, Inc., NJ (2005), ya sea directamente o bien de una manera análoga.

De una manera alternativa, el intermediario H o I se puede

preparar mediante la adición de enolato. Los ejemplos ilustrativos de esta química se ilustran en "Enantioselective Synthesis of ß-amino acids", Segunda Edición, John Wiley and Sons, Inc., NJ (2005), ya sea directamente o bien de una manera análoga.

De una manera alternativa, el intermediario H o I se puede preparar mediante los métodos de la reacción de aza-Michael. Los ejemplos ilustrativos de esta química se ilustran en "Enantioselective Synthesis of ß-amino acids", Segunda Edición, John Wiley and Sons, Inc., NJ (2005), ya sea directamente o bien de una manera análoga.

De una manera alternativa, el intermediario H o I se puede preparar siguiendo la ruta sintética ilustrada en Synlett, 2006, Número 4, páginas 539-542, ya sea directamente o bien de una manera análoga.

La síntesis de los intermediarios J, K y L también se describe en la Solicitud de Patente de los Estados Unidos de Norteamérica del Número de Caso de la Solicitante PAT053600-US-USP3, la cual fue presentada el 16 de abril de 2010, cuya solicitud se incorpora a la presente como referencia.

La invención incluye además cualquier variante de los presentes procesos, en donde se utiliza como material de partida un producto intermediario que se pueda obtener en cualquier etapa de los mismos, y se llevan a cabo los pasos restantes, o en donde los materiales de partida se forman *in situ* bajo las condiciones de reacción, o en donde se utilizan los componentes de la reacción en la forma de sus sales o antípodas ópticamente puros.

Los compuestos de la invención e intermediarios también se pueden convertir unos en otros de acuerdo con los métodos conocidos generalmente por sí mismos.

En otro aspecto, la presente invención proporciona una composición farmacéutica, la cual comprende un compuesto de la presente invención o una sal farmacéuticamente aceptable del mismo, y uno o más vehículos farmacéuticamente aceptables. La composición farmacéutica se puede formular para rutas de administración particulares, tales como administración oral, administración parenteral, y administración rectal, etc. En adición, las composiciones farmacéuticas de la presente invención se pueden hacer en una forma sólida, incluyendo cápsulas, tabletas, píldoras, gránulos, polvos, o supositorios, o en una forma líquida, incluyendo soluciones, suspensiones, o emulsiones. Las composiciones farmacéuticas se pueden someter a operaciones farmacéuticas convencionales, tales como esterilización, y/o pueden contener los diluyentes inertes, agentes de lubricación, o agentes reguladores del pH convencionales, así como adyuvantes, tales como conservadores, estabilizantes, agentes humectantes, emulsionantes, y reguladores del pH, etc.

Típicamente, las composiciones farmacéuticas son tabletas y cápsulas de gelatina que comprenden al ingrediente activo junto con:

a) diluyentes, por ejemplo, lactosa, dextrosa, sacarosa, manitol, sorbitol, celulosa y/o glicina;

b) lubricantes, por ejemplo, sílice, talco, ácido esteárico, su sal de magnesio o calcio, y/o polietilenglicol; para tabletas también

c) aglutinantes, por ejemplo, silicato de magnesio y aluminio, pasta de almidón, gelatina, tragacanto, metil-celulosa, carboxi-metil-celulosa de sodio y/o polivinil-pirrolidona; si se desea

d) desintegrantes, por ejemplo, almidones, ágar, ácido algínico o su sal sódica, o mezclas efervescentes; y/o

e) absorbentes, colorantes, saborizantes y edulcorantes.

Las tabletas pueden tener recubrimiento de película o recubrimiento entérico de acuerdo con los métodos conocidos en este campo.

Las composiciones adecuadas para administración oral incluyen una cantidad efectiva de un compuesto de la invención en la forma de tabletas, grageas, suspensiones acuosas u oleosas, polvos o gránulos dispersables, emulsión, cápsulas duras o blandas, o jarabes o elíxires. Las composiciones pretendidas para uso oral se preparan de acuerdo con cualquier método conocido en la técnica para la elaboración de composiciones farmacéuticas, y estas composiciones pueden contener uno o más agentes seleccionados a partir del grupo que consiste en agentes edulcorantes, agentes saborizantes, agentes colorantes, y agentes conservadores, con el objeto de proporcionar preparaciones farmacéuticamente elegantes y

de buen sabor. Las tabletas contienen al ingrediente activo mezclado con excipientes farmacéuticamente aceptables no tóxicos que sean adecuados para la elaboración de tabletas. Estos excipientes son, por ejemplo, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio, o fosfato de sodio; agentes de granulación o desintegrantes, por ejemplo almidón de maíz, o ácido algínico; agentes aglutinantes, por ejemplo almidón, gelatina, o acacia; y agentes lubricantes, por ejemplo estearato de magnesio, ácido esteárico, o talco. Las tabletas no se recubren, o bien se recubren mediante técnicas conocidas para demorar la desintegración y absorción en el tracto gastrointestinal y de esta manera proporcionar una acción sostenida durante un período más largo. Por ejemplo, se puede emplear un material de demora de tiempo tal como monestearato de glicerilo o diestearato de glicerilo. Las formulaciones para uso oral se pueden presentar como cápsulas de gelatina dura en donde se mezcla el ingrediente activo con un diluyente sólido inerte, por ejemplo carbonato de calcio, fosfato de calcio, o caolín, o como cápsulas de gelatina blanda en donde se mezcla el ingrediente activo con agua o con un medio oleoso, por ejemplo aceite de cacahuate, parafina líquida, o aceite de oliva.

Ciertas composiciones inyectables son soluciones o suspensiones isotónicas acuosas, y los supositorios convenientemente se preparan a partir de emulsiones o suspensiones grasas. Estas composiciones se pueden esterilizar y/o pueden contener adyuvantes, tales como agentes conservadores,

estabilizantes, humectantes, o emulsionantes, promotores de solución, sales para regular la presión osmótica, y/o reguladores del pH. En adición, también pueden contener otras sustancias terapéuticamente valiosas. Estas composiciones se preparan de acuerdo con los métodos convencionales de mezcla, granulación, o recubrimiento, respectivamente, y pueden contener de aproximadamente el 0.1 al 75 por ciento, o contienen de aproximadamente el 1 al 50 por ciento del ingrediente activo.

Las composiciones adecuadas para aplicación transdérmica incluyen una cantidad efectiva de un compuesto de la invención con un vehiculo. Los vehiculos incluyen solventes farmacológicamente aceptables absorbibles para ayudar al paso a través de la piel del huésped. Por ejemplo, los dispositivos transdérmicos están en la forma de un parche, el cual comprende un miembro de respaldo, un depósito que contiene al compuesto opcionalmente con vehículos, opcionalmente una barrera de control de velocidad para suministrar el compuesto a la piel del huésped a una velocidad controlada y previamente determinada durante un período de tiempo prolongado, y elementos para asegurar el dispositivo a la piel.

Las composiciones adecuadas para aplicación tópica, por ejemplo a la piel y a los ojos, incluyen soluciones acuosas, suspensiones, ungüentos, cremas, geles, o formulaciones rociables, por ejemplo para suministrarse en aerosol o similar. Estos sistemas de suministro tópico serán apropiados en particular para aplicación dérmica. De esta manera, son particularmente adecuadas para

utilizarse en formulaciones tópicas, incluyendo cosméticas, bien conocidas en este campo. Éstas pueden contener solubilizantes, estabilizantes, agentes mejoradores de tonicidad, reguladores del pH, y conservadores.

Como se utiliza en la presente, una aplicación tópica también puede pertenecer a una inhalación o a una aplicación intranasal. De una manera conveniente, se suministran en la forman de un polvo seco (ya sea solo, como una mezcla, por ejemplo una mezcla seca con lactosa, o bien como una partícula componente mezclada, por ejemplo con fosfolípidos) a partir de un inhalador de polvo seco o de una presentación de aspersión en aerosol a partir de un recipiente presurizado, bomba, aspersor, atomizador o nebulizador, con o sin el uso de un propelente adecuado.

La presente invención proporciona además composiciones farmacéuticas y formas de dosificación anhidras, las cuales comprenden los compuestos de la presente invención como ingredientes activos, debido a que el agua puede facilitar la degradación de ciertos compuestos.

Se pueden preparar composiciones farmacéuticas anhidras y formas de dosificación de la invención utilizando ingredientes anhidros o que contengan una baja humedad, y condiciones de baja humedad. Una composición farmacéutica anhidra se puede preparar y almacenar de tal manera que se mantenga su naturaleza anhidra. De conformidad con lo anterior, las composiciones anhidras de preferencia se empacan utilizando materiales que se sepa que

previenen la exposición al agua, de tal forma que se puedan incluir en kits de formulación adecuados. Los ejemplos del empaque adecuado incluyen, pero no se limitan a, láminas herméticamente selladas, plásticos, recipientes de dosis unitaria (por ejemplo, frascos), paquetes de burbuja, y paquetes de tiras.

La invención proporciona además composiciones farmacéuticas y formas de dosificación que comprenden uno o más agentes que reducen la velocidad a la cual se descompondrá el compuesto de la presente invención como un ingrediente activo. Estos agentes, los cuales son referidos en la presente como "estabilizantes", incluyen, pero no se limitan a, antioxidantes, tales como ácido ascórbico, reguladores del pH, o reguladores de sales, etc.

Los compuestos de acuerdo con cualquiera de las fórmulas I' y I a VIIC, en forma libre o en forma de sal farmacéuticamente aceptable, exhiben valiosas propiedades farmacológicas, por ejemplo, propiedades moduladoras de la endopeptidasa neutra EC 3.4. 24.11, por ejemplo, como se indica en las pruebas *in vitro* e *in vivo* proporcionadas en las siguientes secciones y, por consiguiente, se indican para terapia.

Los compuestos de la invención, o una sal farmacéuticamente aceptable de los mismos, pueden ser útiles en el tratamiento de una indicación seleccionada a partir de: trastornos cardiovasculares, tales como hipertensión, hipertensión pulmonar, hipertensión sistólica aislada, hipertensión resistente, enfermedad vascular periférica, insuficiencia cardíaca, insuficiencia cardíaca congestiva,

hipertrofia de ventrículo izquierdo, angina, insuficiencia renal, falla renal (incluyendo edema y retención de sal), nefropatía diabética, nefropatía no diabética, edema cíclico, enfermedad de Menières, hiperaldosteronismo (primario y secundario) e hipercalciuria, ascitas, glaucoma, trastornos menstruales, parto a pretérmino, pre-eclampsia, endometriosis, y trastornos reproductivos (en especial infertilidad masculina y femenina, síndrome de ovario poliquístico, fracaso de implante), asma, apnea obstructiva del sueño, inflamación, leucemia, dolor, epilepsia, trastornos afectivos, tales como depresión y condición psicótica, tal como demencia y confusión geriátrica, obesidad y trastornos gastrointestinales (en especial diarrea y síndrome de intestino irritable), sanado de heridas (en especial úlceras diabéticas y venosas, y llagas por decúbito), choque séptico, modulación de secreción de ácido gástrico, tratamiento de hiperreninemia, fibrosis quística, restenosis, diabetes tipo 2, complicaciones diabéticas y ateroesclerosis, disfunción sexual masculina y femenina.

Por consiguiente, como una modalidad adicional, la presente invención proporciona el uso de un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo. En una modalidad adicional, la terapia se selecciona a partir de una enfermedad que se mitiga mediante la inhibición de la endopeptidasa neutra EC 3.4. 24.11. En otra modalidad, la enfermedad se selecciona a partir de la lista anteriormente mencionada, de una manera adecuada hipertensión,

hipertensión pulmonar, hipertensión sistólica aislada, hipertensión resistente, enfermedad vascular periférica, insuficiencia cardíaca, insuficiencia cardíaca congestiva, hipertrofia de ventrículo izquierdo, angina, insuficiencia renal, falla renal (incluyendo edema y retención de sal), nefropatía diabética, nefropatía no diabética, diabetes tipo 2, y complicaciones diabéticas, y de una manera más adecuada, trastornos cardiovasculares, tales como hipertensión, insuficiencia renal, incluyendo edema, e insuficiencia cardíaca congestiva.

En otra modalidad, la invención proporciona un método para el tratamiento de una enfermedad que se mitiga mediante la inhibición de la endopeptidasa neutra EC 3.4. 24.11, el cual comprende la administración de una cantidad terapéuticamente aceptable de un compuesto de acuerdo con cualquiera de las fórmulas I', I, IA, II, IIA, III, IIIA, IV, IVA, V, VA, VI, VIA, y VII a VIIC, o una sal farmacéuticamente aceptable del mismo. En una modalidad adicional, la enfermedad se selecciona a partir de la lista anteriormente mencionada, de una manera adecuada hipertensión, hipertensión pulmonar, hipertensión sistólica aislada, hipertensión resistente, enfermedad vascular periférica, insuficiencia cardíaca, insuficiencia cardíaca congestiva, hipertrofia de ventrículo izquierdo, angina, insuficiencia renal, falla renal (incluyendo edema y retención de sal), nefropatía diabética, nefropatía no diabética, diabetes tipo 2, y complicaciones diabéticas, y de una manera más adecuada, trastornos cardiovasculares, tales como hipertensión, insuficiencia renal, incluyendo edema, e insuficiencia cardíaca congestiva.

La composición o combinación farmacéutica de la presente invención puede estar en una dosificación unitaria de aproximadamente 1 a 1,000 miligramos de ingrediente(s) activo(s) para un sujeto de aproximadamente 50 a 70 kilogramos, o de aproximadamente 1 a 500 miligramos, o de aproximadamente 1 a 250 miligramos, o de aproximadamente 1 a 150 miligramos, o de aproximadamente 0.5 a 100 miligramos, o de aproximadamente 1 a 50 miligramos de ingredientes activos. La dosificación terapéuticamente efectiva de un compuesto, de la composición farmacéutica, o de las combinaciones de los mismos, depende de la especie del sujeto, del peso corporal, de la edad y condición individual, del trastorno o enfermedad que se esté tratando, o de la gravedad de la misma. Un médico, clínico, o veterinario de una experiencia ordinaria puede determinar fácilmente la cantidad efectiva de cada uno de los ingredientes activos necesaria para prevenir, tratar, o inhibir el progreso del trastorno o de la enfermedad.

Las propiedades de dosificación anteriormente citadas se pueden demostrar en pruebas *in vitro* e *in vivo* utilizando convenientemente mamíferos, por ejemplo, ratones, ratas, perros, monos u órganos aislados, tejidos, y preparaciones de los mismos. Los compuestos de la presente invención se pueden aplicar *in vitro* en la forma de soluciones, por ejemplo, de preferencia soluciones acuosas, e *in vivo* ya sea enteralmente, parenteralmente, de una

manera conveniente intravenosamente, por ejemplo, como una suspensión o en solución acuosa. La dosificación *in vitro* puede estar en el intervalo de concentraciones de entre aproximadamente 10^{-3} molar y 10^{-9} molar. Una cantidad terapéuticamente efectiva *in vivo* dependiendo de la vía de administración, puede estar en el intervalo de entre aproximadamente 0.1 y 500 miligramos/kilogramo, o de entre aproximadamente 1 y 100 miligramos/kilogramo.

La actividad de un compuesto de acuerdo con la presente invención se pueden evaluar mediante los siguientes métodos *in vitro* e *in vivo* y/o mediante los métodos *in vitro* e *in vivo* bien descritos en la técnica. Véase, A fluorescence lifetime-based assay for protease inhibitor profiling on human kallikrein 7 Doering K, Meder G, Hinnenberger M, Woelcke J, Mayr LM, Hassiepen U Biomol Screen. Enero de 2009; 14(1):1-9.

En particular, la inhibición *in vitro* de la endopeptidasa neutra humana recombinante (NEP, EC 3.4.24.11) se puede determinar como sigue:

La endopeptidasa neutra humana recombinante (expresada en células de insecto y purificada empleando los métodos convencionales, concentración final de 7 pM) se incuba previamente con los compuestos de prueba en diferentes concentraciones durante 1 hora a temperatura ambiente en regulador de fosfato de sodio 10 mM a un pH de 7.4, que contiene NaCl 150 mM y CHAPS al 0.05 por ciento (peso/volumen). La reacción enzimática se inicia mediante la adición del sustrato peptídico sintético de Cys(PT14)-Arg-Arg-Leu-

Trp-OH hasta una concentración final de 0.7 µM. La hidrólisis del sustrato conduce a un aumento en el tiempo de vida de la fluorescencia (FLT) del PT14 medido por medio de un lector de FLT como es descrito por Doering y colaboradores (2009). El efecto del compuesto sobre la actividad enzimática se determinó después de una incubación durante 1 hora (t = 60 minutos) a temperatura ambiente. Los valores IC_{50}, correspondientes a la concentración del inhibidor que muestra una reducción del 50 por ciento de los valores FLT medidos en ausencia del inhibidor, se calculan a partir de la gráfica de porcentaje de inhibición contra concentración de inhibidor, utilizando el software de análisis de regresión no lineal.

Empleando en ensayo de prueba (como se describe anteriormente), los compuestos de la invención exhibieron una eficacia inhibidora de acuerdo con la Tabla 1 proporcionada en seguida.

Tabla 1

Actividad Inhibidora de los Compuestos

Ejemplo #	**NEP Humana - IC_{50} (nM)**
Ejemplo 3-25	18
Ejemplo 3-26	15
Ejemplo 3-27	15
Ejemplo 5-1	38

Ejemplo #	NEP Humana - IC_{50} (nM)
Ejemplo 5-4	7
Ejemplo 5-7	4
Ejemplo 5-11	3
Ejemplo 5-12	67
Ejemplo 5-36	42
Ejemplo 5-37	2.3
Ejemplo 5-39	0.7
Ejemplo 5-46	0.5
Ejemplo 5-47	2.7
Ejemplo 5-55	0.7
Ejemplo 6-1	75
Ejemplo 9-1	56
Ejemplo 11-1	1.1
Ejemplo 11-11	0.5
Ejemplo 11-14	0.07
Ejemplo 12-1	0.2

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Ejemplo #	NEP Humana - IC_{50} (nM)
Ejemplo 14-1	0.8
Ejemplo 15-1	1.2

El compuesto de la presente invención se puede administrar ya sea de una manera simultánea con, o antes, o después, de cuando menos otro agente terapéutico. El compuesto de la presente invención se puede administrar por separado, por la misma o diferente vía de administración, o juntos en la misma composición farmacéutica.

En una modalidad, la invención proporciona un producto que comprende un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, y cuando menos otro agente terapéutico, como una preparación combinada para su uso simultáneo, separado, o en secuencia, en terapia. En una modalidad, la terapia es el tratamiento de una enfermedad o condición asociada con la actividad de la endopeptidasa neutra EC 3.4. 24.11. Los productos proporcionados como una preparación combinada incluyen una composición que comprende al compuesto de las fórmulas I' y I a VIIC y los otros agentes terapéuticos juntos en la misma composición farmacéutica, o al compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, y los otros

agentes terapéuticos en una forma separada, por ejemplo, en la forma de un kit.

En una modalidad, la invención proporciona una composición farmacéutica, la cual comprende un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, y otros agentes terapéuticos. Opcionalmente, la composición farmacéutica puede comprender un excipiente farmacéuticamente aceptable, como se describe anteriormente.

En una modalidad, la invención proporciona un kit, el cual comprende dos o más composiciones farmacéuticas separadas, cuando menos una que contenga un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo. En una modalidad, el kit comprende medios para conservar por separado estas composiciones, tales como un recipiente, un frasco dividido, o un paquete de lámina dividido. Un ejemplo de este kit es un paquete de burbuja, como se utiliza típicamente para el empaque de tabletas, cápsulas y similares.

El kit de la invención se puede utilizar para administrar diferentes formas de dosificación, por ejemplo, oral y parenteral, para administrar las composiciones separadas en diferentes intervalos de dosificación, o para titular las composiciones separadas una contra la otra. Con el objeto de ayudar al cumplimiento, el kit de la invención típicamente comprende instrucciones para su administración.

En las terapias de combinación de la invención, el compuesto

de la invención, o una sal farmacéuticamente aceptable del mismo, y el otro agente terapéutico pueden ser elaborados y/o formulados por el mismo o por diferentes fabricantes. Más aún, el compuesto de la invención, o una sal farmacéuticamente aceptable del mismo, y el otro agente terapéutico, se pueden reunir en una terapia de combinación: (i) antes de expedir el producto de combinación a los médicos (por ejemplo, en el caso de un kit, el cual comprende el compuesto de la invención y el otro agente terapéutico); (ii) por los médicos mismos (o bajo la guía del médico) poco antes de su administración; (iii) por los pacientes mismos, por ejemplo, durante la administración en secuencia del compuesto de la invención y el otro agente terapéutico.

De conformidad con lo anterior, la invención proporciona el uso de un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, en la elaboración de un medicamento para el tratamiento de una enfermedad o condición asociada con la actividad de la endopeptidasa neutra EC 3.4. 24.11, en donde el medicamento se prepara para su administración con otro agente terapéutico. La invención también proporciona el uso de otro agente terapéutico en la elaboración de un medicamento para el tratamiento de una enfermedad o condición asociada con la actividad de la endopeptidasa neutra EC 3.4. 24.11, en donde el medicamento se prepara para su administración con un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente

aceptable del mismo.

La invención también proporciona un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, para utilizarse en un método para el tratamiento de una enfermedad o condición asociada con la actividad de la endopeptidasa neutra EC 3.4. 24.11, en donde el compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, se prepara para su administración con otro agente terapéutico. La invención también proporciona otro agente terapéutico para utilizarse en un método para el tratamiento de una enfermedad o condición asociada con la actividad de la endopeptidasa neutra EC 3.4. 24.11, en donde el otro agente terapéutico se prepara para su administración con un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo. La invención también proporciona un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, para utilizarse en un método para el tratamiento de una enfermedad o condición asociada con la actividad de la endopeptidasa neutra EC 3.4. 24.11, en donde el compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, se administra con otro agente terapéutico. La invención también proporciona otro agente terapéutico para utilizarse en un método para el tratamiento de una enfermedad o condición asociada con la actividad de la

endopeptidasa neutra EC 3.4. 24.11, en donde el otro agente terapéutico se administra con un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo.

La invención también proporciona el uso de un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo, en la elaboración de un medicamento para el tratamiento de una enfermedad o condición asociada con la actividad de la endopeptidasa neutra EC 3.4. 24.11, en donde el paciente ha sido tratado previamente (por ejemplo, dentro de 24 horas) con otro agente terapéutico. La invención también proporciona el uso de otro agente terapéutico en la elaboración de un medicamento para el tratamiento de una enfermedad o condición asociada con la actividad de la endopeptidasa neutra EC 3.4. 24.11, en donde el paciente ha sido tratado previamente (por ejemplo, dentro de 24 horas) con un compuesto de acuerdo con cualquiera de las fórmulas I' y I a VIIC, o una sal farmacéuticamente aceptable del mismo.

En una modalidad, el otro agente terapéutico se selecciona a partir de: un inhibidor de HMG-Co-A-reductasa, un bloqueador de los receptores de angiotensina (ARBs, antagonista de los receptores de angiotensina II), un inhibidor de la enzima convertidora de angiotensina (ACE), un bloqueador del canal de calcio (CCB), un antagonista de endotelina, un inhibidor de renina, un diurético, un mimético de ApoA-I, un agente anti-diabético, un agente reductor de

la obesidad, un bloqueador de los receptores de aldosterona, un bloqueador de los receptores de endotelina, un inhibidor de sintasa de aldosterona (ASI), un inhibidor de CETP, o un inhibidor de fosfodiesterasa 5 (PDE5).

El término "en combinación con" un segundo agente o tratamiento incluye la co-administración del compuesto de la invención (por ejemplo, un compuesto de las fórmulas I' o I-VIIC, o un compuesto descrito de otra manera en la presente) con el segundo agente o tratamiento, la administración del compuesto de la invención primero, seguido por el segundo agente o tratamiento, y la administración del segundo agente o tratamiento primero, seguido por el compuesto de la invención.

El término "segundo agente" incluye cualquier agente que se conozca en la materia para tratar, prevenir, o reducir los síntomas de una enfermedad o trastorno descrito en la presente, por ejemplo, un trastorno o enfermedad que responda a la inhibición de la endopeptidasa neutra, tal como, por ejemplo, hipertensión, hipertensión pulmonar, hipertensión sistólica aislada, hipertensión resistente, enfermedad vascular periférica, insuficiencia cardíaca, insuficiencia cardíaca congestiva, hipertrofia de ventrículo izquierdo, angina, insuficiencia renal (diabética o no diabética), falla renal (incluyendo edema y retención de sal), nefropatía diabética, nefropatía no diabética, síndrome nefrótico, glomerulonefritis, esclerodermia, esclerosis glomerular, proteinuria de enfermedad renal primaria, hipertensión vascular renal, retinopatía diabética y

enfermedad renal en etapa final (ESRD), disfunción endotelial, disfunción diastólica, cardiomiopatía hipertrófica, miopatía cardíaca diabética, arritmias supraventriculares y ventriculares, fibrilación auricular (AF), fibrosis cardíaca, flúter auricular, remodelación vascular perjudicial, estabilización de placa, infarto de miocardio (MI), fibrosis renal, enfermedad de riñón poliquístico (PKD), hipertensión arterial pulmonar, falla renal (incluyendo edema y retención de sal), edema cíclico, enfermedad de Menières, hiperaldosteronismo (primario y secundario) e hipercalciuria, ascitas, glaucoma, trastornos menstruales, parto a pretérmino, pre-eclampsia, endometriosis, y trastornos reproductivos (en especial infertilidad masculina y femenina, síndrome de ovario poliquístico, fracaso de implante), asma, apnea obstructiva del sueño, inflamación, leucemia, dolor, epilepsia, trastornos afectivos, tales como depresión y condición psicótica, tal como demencia y confusión geriátrica, obesidad y trastornos gastrointestinales (en especial diarrea y síndrome de intestino irritable), sanado de heridas (en especial úlceras diabéticas y venosas, y llagas por decúbito), choque séptico, disfunción de secreción de ácido gástrico, hiperreninemia, fibrosis quística, restenosis, diabetes tipo 2, síndrome metabólico, complicaciones diabéticas y ateroesclerosis, disfunción sexual masculina y femenina.

Los ejemplos de los segundos agentes incluyen inhibidores de HMG-Co-A-reductasa, antagonistas de los receptores de angiotensina II, inhibidores de la enzima convertidora de

angiotensina (ACE), bloqueadores del canal de calcio (CCB), antagonistas de endotelina, inhibidores de renina, diuréticos, miméticos de ApoA-I, agentes anti-diabéticos, agentes reductores de la obesidad, bloqueadores de los receptores de aldosterona, bloqueadores de los receptores de endotelina, inhibidores de sintasa de aldosterona (ASI), e inhibidores de CETP.

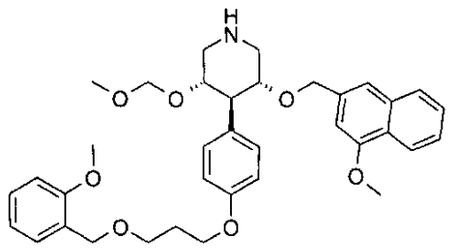
El término "inhibidores de HMG-Co-A-reductasa" (también denominados como inhibidores de ß-hidroxi-ß-metil-glutaril-co-enzima-A-reductasa) incluye los agentes activos que se pueden utilizar para reducir los niveles de lípido, incluyendo el colesterol en sangre. Los ejemplos incluyen atorvastatina, cerivastatina, compactina, dalvastatina, dihidrocompactina, fluindostatina, fluvastatina, lovastatina, pitavastatina, mevastatina, pravastatina, rivastatina, simvastatina, y velostatina, o las sales farmacéuticamente aceptables de las mismas.

El término "inhibidor de ACE" (también denominado como inhibidor de la enzima convertidora de angiotensina) incluye las moléculas que interrumpen la degradación enzimática de la angiotensina I hasta la angiotensina II. Estos compuestos se pueden utilizar para la regulación de la presión arterial, y para el tratamiento de insuficiencia cardíaca congestiva. Los ejemplos incluyen alacepril, benazepril, benazeprilato, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilato, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, y trandolapril, o las sales farmacéuticamente aceptables de los mismos.

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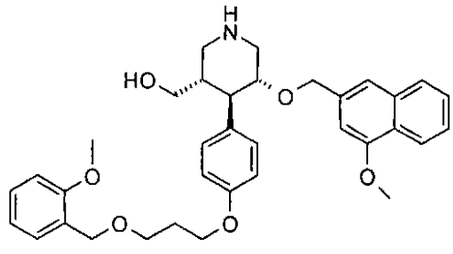
El término "antagonista de endotelina" incluye bosentan (véase la Patente Europea Número EP 526708 A), tezosentan (véase la Publicación Internacional Número WO 96/19459), o las sales farmacéuticamente aceptables de los mismos.

El término "inhibidor de renina" incluye ditequireno (nombre químico: [1*S*-[1*R**,2*R**,4*R**(1*R**,2*R**)]]-1-[(1,1-dimetil-etoxi)-carbonil]-L-prolil-L-fenilalanil-N-[2-hidroxi-5-metil-1-(2-metil-propil)-4-[[[2-metil-1-[[(2-piridinil-metil)-amino]-carbonil]-butil]-amino]-carbonil]-hexil]-*N*-alfa-metil-L-histidinamida); terlaquireno (nombre químico: [*R*-(*R**,*S**)]-N-(4-morfolinil-carbonil)-1-fenilalanil-N-[1-(ciclohexil-metil)-2-hidroxi-3-(1-metil-etoxi)-3-oxopropil]-S-metil-L-cisteinamida); Alisquireno (nombre químico: (2*S*,4*S*,5*S*,7*S*)-5-amino-*N*-(2-carbamoil-2,2-dimetil-etil)-4-hidroxi-7-{[4-metoxi-3-(3-metoxi-propoxi)-fenil]-metil}-8-metil-2-(propan-2-il)-nonanamida), y zanquireno (nombre químico: [1*S*-[1*R**[*R**(*R**)],2*S**,3*R**]]-*N*-[1-(ciclohexil-metil)-2,3-dihidroxi-5-metil-hexil]-alfa-[[2-[[(4-metil-1-piperazinil)-sulfonil]-metil]-1-oxo-3-fenil-propil]-amino]-4-tiazol-propanamida), o las sales de clorhidrato de los mismos, o SPP630, SPP635 y SPP800 como son desarrollados por Speedel, o RO 66-1132 y RO 66-1168 de las fórmulas (A) y (B):



(A)

y



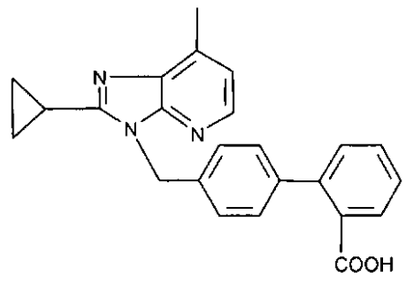
(B)

o las sales farmacéuticamente aceptables de los mismos.

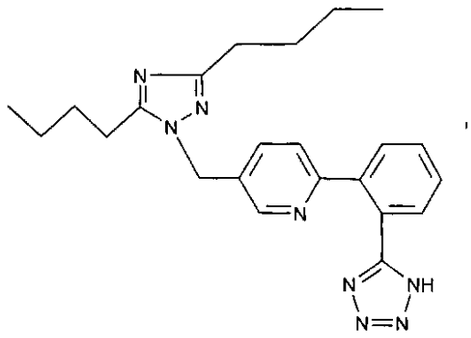
El término "alisquireno", si no se define de una manera específica, se debe entender como la base libre así como una sal del mismo, en especial una sal farmacéuticamente aceptable del mismo, más preferiblemente una sal de hemi-fumarato del mismo.

Se entiende que un antagonista de los receptores de angiotensina II o una sal farmacéuticamente aceptable del mismo, es un ingrediente activo que se enlaza al subtipo del receptor AT_1 de los receptores de angiotensina II, pero no dan como resultado la activación del receptor. Como una consecuencia de la inhibición del receptor AT_1, estos antagonistas, por ejemplo, se pueden emplear como anti-hipertensivos, o para el tratamiento de insuficiencia cardíaca congestiva.

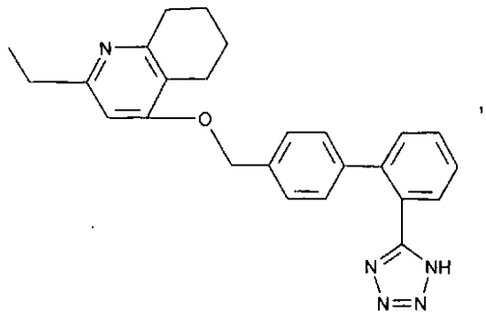
La clase de antagonistas del receptor AT_1 comprende los compuestos que tienen diferentes características estructurales, y se prefieren esencialmente los no peptídicos. Por ejemplo, se puede hacer mención de los compuestos que se seleccionan a partir del grupo que consiste en valsartan, losartan, candesartan, eprosartan, irbesartan, saprisartan, tasosartan, telmisartan, el compuesto con la designación E-1477 de la siguiente fórmula:



el compuesto con la designación SC-52458 de la siguiente fórmula:



y el compuesto con la designación ZD-8731 de la siguiente fórmula:



o, en cada caso, una sal farmacéuticamente aceptable del mismo.

Los antagonistas de los receptores AT_1 preferidos son los agentes que se han comerciado, , más preferiblemente valsartan o una sal farmacéuticamente aceptable del mismo.

El término "un bloqueador del canal de calcio (CCB)" incluye dihidro-piridinas (DHPs), y no dihidro-piridinas (no DHPs) (por

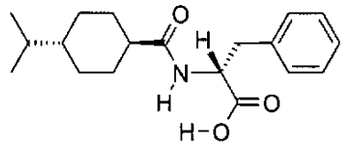
ejemplo, los bloqueadores del canal de calcio (CCBs) de tipo dil-tiazem y de tipo verapamil). Los ejemplos incluyen amlodipina, felodipina, riosidina, isradipina, lacidipina, nicardipina, nifedipina, niguldipina, niludipina, nimodipina, nisoldipina, nitrendipina, y nivaldipina, y es de preferencia un representante de no dihidro-piridinas (no DHPs) seleccionado a partir del grupo que consiste en flunarizina, prenilamina, dil-tiazem, fendilina, galopamil, mibefradil, anipamil, tiapamil y verapamil, o las sales farmacéuticamente aceptables de los mismos. Los bloqueadores del canal de calcio (CCBs) se pueden utilizar como fármacos contra la hipertensión, contra la angina de pecho, o anti-arrítmicos.

El término "diurético" incluye los derivados de tiazida (por ejemplo, clorotiazida, hidroclorotiazida, metilclotiazida, y cloro-talidona).

El término "mimético de ApoA-I" incluye los péptidos D4F (por ejemplo, de la fórmula D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F).

El término "agente anti-diabético" incluye los potenciadores de la secreción de insulina que promueven la secreción de insulina a partir de las células-ß pancreáticas. Los ejemplos incluyen los derivados de biguanida (por ejemplo, metformina), sulfonil-ureas (SU) (por ejemplo, tolbutamida, clorpropamida, tolazamida, acetohexamida, 4-cloro-*N*-[(1-pirrolidinil-amino)-carbonil]-bencen-sulfonamida (glicopiramida), glibenclamida (gliburida), gliclazida, 1-butil-3-metanilil-urea, carbutamida, glibonurida, glipizida, gliquidona, glisoxepida, glibutiazol, glibuzol, glihexamida, glimidina, glipinamida,

fenbutamida, y tolil-ciclamida), o las sales farmacéuticamente aceptables de los mismos. Otros ejemplos incluyen los derivados de fenilalanina (por ejemplo, nateglinida [*N*-(*trans*-4-isopropil-ciclohexil-carbonil)-*D*-fenilalanina] (véanse las Patentes Europeas Números EP 196222 y EP 526171) de la fórmula:



);

repaglinida [ácido (*S*)-2-etoxi-4-{2-[[3-metil-1-[2-(1-piperidinil)-fenil]-butil]-amino]-2-oxo-etil}-benzoico] (véanse las Patentes Europeas Números EP 589874, EP 147850 A2, en particular el Ejemplo 11 de la página 61, y la Patente Europea Número EP 207331 A1); dihidrato de (2*S*)-2-bencil-3-(*cis*-hexahidro-2-isoindolinil-carbonil)-propionato de calcio (por ejemplo, mitiglinida (véase la Patente Europea Número EP 507534)); y glimepirida (véase la Patente Europea Número EP 31058). Otros ejemplos incluyen los inhibidores de DPP-IV, GLP-1 y agonistas de GLP-1.

DPP-IV es responsable de la inactivación de GLP-1. De una manera más particular, DPP-IV genera un antagonista de los receptores de GLP-1, y de esta manera, reduce la respuesta fisiológica al GLP-1. GLP-1 es un estimulante mayor de la secreción de la insulina pancreática, y tiene efectos benéficos directos sobre la eliminación de la glucosa.

El inhibidor de DPP-IV puede ser peptídico o, de preferencia, no peptídico. Los inhibidores de DPP-IV se dan a conocer en cada caso de una manera genérica y específica, por ejemplo, en las Patentes Números WO 98/19998, DE 196 16 486 A1, WO 00/34241 y WO 95/15309, en cada caso en particular en las reivindicaciones de compuestos, y los productos finales de los ejemplos de procesamiento, el asunto objeto de los productos finales, las preparaciones farmacéuticas, y las reivindicaciones, se incorporan a la presente solicitud por referencia a estas publicaciones. Se prefieren los compuestos que se dan a conocer específicamente en el Ejemplo 3 de la Publicación Internacional Número WO 98/19998, y en el Ejemplo 1 de la Publicación Internacional Número WO 00/34241, respectivamente.

GLP-1 es una proteína insulinotrópica que es descrita, por ejemplo, por W. E. Schmidt y colaboradores, en *Diabetologia*, 28, 1985, 704-707 y en la Patente de los Estados Unidos de Norteamérica Número US 5,705,483.

El término "agonistas de GLP-1" incluye las variantes y los análogos de GLP-1(7-36)NH_2 los cuales se dan a conocer en particular en las Patentes de los Estados Unidos de Norteamérica Números US 5,120,712, US 5,118666, y US 5,512,549, en la Publicación Internacional Número WO 91/11457, y por C. Orskov y colaboradores, en J. Biol. Chem. 264 (1989) 12826. Otros ejemplos incluyen GLP-1(7-37), en cuyo compuesto, la funcionalidad de amida carboxi-terminal de Arg^{36} es desplazada con Gly en la posición 37 de

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la molécula de GLP-1(7-36)NH_2 y las variantes y los análogos de la misma, incluyendo GLN^9-GLP-1(7-37), D-GLN^9-GLP-1(7-37), acetil-LYS^9-GLP-1(7-37), LYS^{18}-GLP-1(7-37) y, en particular, GLP-1(7-37)OH, VAL^8-GLP-1(7-37), GLY^8-GLP-1(7-37), THR^8-GLP-1(7-37), MET^8-GLP-1(7-37), y 4-imidazo-propionil-GLP-1. También se da una preferencia especial al análogo del agonista de GLP exendina-4, descrita por Greig y colaboradores en *Diabetologia* 1999, 42, 45-50.

En la definición de "agente anti-diabético" también se incluyen los potenciadores de la sensibilidad a la insulina que restablecen la función deteriorada del receptor de insulina para reducir la resistencia a la insulina y, en consecuencia, para potenciar la sensibilidad a la insulina. Los ejemplos incluyen los derivados de la tiazolidinadiona hipoglicémica (por ejemplo, glitazona), (S)-((3,4-dihidro-2-(fenil-metil)-2H-1-benzopiran-6-il)-metil-tiazolidina-2,4-diona (englitazona), 5-{[4-(3-(5-metil-2-fenil-4-oxazolil)-1-oxopropil)-fenil]-metil}-tiazolidina-2,4-diona (darglitazona), 5-{[4-(1-metil-ciclohexil)-metoxi)-fenil]-metil}-tiazolidina-2,4-diona (ciglitazona), 5-{[4-(2-(1-indolil)-etoxi)-fenil]-metil}-tiazolidina-2,4-diona (DRF2189), 5-{4-[2-(5-metil-2-fenil-4-oxazolil)-etoxi)]-bencil}-tiazolidina-2,4-diona (BM-13.1246), 5-(2-naftil-sulfonil)-tiazolidina-2,4-diona (AY-31637), bis-{4-[(2,4-dioxo-5-tiazolidinil)-metil]-fenil}-metano (YM268), 5-{4-[2-(5-metil-2-fenil-4-oxazolil)-2-hidroxi-etoxi]-bencil}-tiazolidina-2,4-diona (AD-5075), 5-[4-(1-fenil-1-ciclopropan-carbonil-amino)-bencil]-tiazolidina-2,4-diona (DN-108) 5-{[4-(2-(2,3-dihidro-indol-1-il)-etoxi)-fenil]-metil}-tiazolidina-2,4-diona, 5-[3-(4-cloro-fenil])-2-propinil]-5-

fenil-sulfonil)-tiazolidina-2,4-diona, 5-[3-(4-cloro-fenil])-2-propinil]-5-(4-fluoro-fenil-sulfonil)-tiazolidina-2,4-diona, 5-{[4-(2-(metil-2-piridinil-amino)-etoxi)-fenil]-metil}-tiazolidina-2,4-diona (rosiglitazona), 5-{[4-(2-(5-etil-2-piridil)-etoxi)-fenil]-metil}-tiazolidina-2,4-diona (pioglitazona), 5-{[4-((3,4-dihidro-6-hidroxi-2,5,7,8-tetrametil-2H-1-benzopiran-2-il)-metoxi)-fenil]-metil}-tiazolidina-2,4-diona (troglitazona), 5-[6-(2-fluoro-benciloxi)-naftalen-2-il-metil]-tiazolidina-2,4-diona (MCC555), 5-{[2-(2-naftil)-benzoxazol-5-il]-metil}-tiazolidina-2,4-diona (T-174), y 5-(2,4-dioxo-tiazolidin-5-il-metil)-2-metoxi-N-(4-trifluoro-metil-bencil)-benzamida (KRP297)).

Otros agentes anti-diabéticos incluyen a los moduladores de la senda de señalización de insulina, como los inhibidores de fosfatasas de proteína tirosina (PTPasas), compuestos miméticos de moléculas no pequeñas anti-diabéticos, e inhibidores de amido-transferasa de glutamina-fructosa-6-fosfato (GFAT); compuestos que tienen influencia sobre la producción desregulada de la glucosa hepática, como los inhibidores de glucosa-6-fosfatasa (G6Pasa), los inhibidores de fructosa-1,6-bisfosfatasa (F-1,6-Bpasa), los inhibidores de fosforilasa de glicógeno (GP), antagonistas de los receptores de glucagon, e inhibidores de carboxicinasa de piruvato de fosfoenol (PEPCK); inhibidores de cinasa de deshidrogenasa de piruvato (PDHK); inhibidores del vaciado gástrico; insulina; inhibidores de GSK-3; agonistas del receptor retinoide X (RXR); agonistas de Beta-3 AR; agonistas de las proteínas de desacoplamiento (UCPs); agonistas de PPARγ no de tipo glitazona;

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agonistas dobles de PPARα/ PPARγ; compuestos anti-diabéticos que contienen vanadio; hormonas de incretina, como el péptido tipo glucagon-1 (GLP-1), y los agonistas de GLP-1; antagonistas de los receptores de imidazolina de las células-beta; miglitol; antagonistas α_2-adrenérgicos; y las sales farmacéuticamente aceptables de los mismos.

El término "agente reductor de la obesidad" incluye los inhibidores de lipasa (por ejemplo, orlistato), y a los supresores del apetito (por ejemplo, sibutramina y fentermina).

Se entiende que un inhibidor de la sintasa de aldosterona o una sal farmacéuticamente aceptable del mismo es un ingrediente activo que tiene la propiedad para inhibir la producción de aldosterona. La sintasa de aldosterona (CYP11B2) es una enzima del citocromo P450 mitocondrial que cataliza el último paso de la producción de aldosterona en la corteza suprarrenal, es decir, la conversión de la 11-desoxicorticosterona hasta aldosterona. Se sabe que la inhibición de la producción de aldosterona con los denominados inhibidores de sintasa de aldosterona es una variante de éxito para el rataiento de hipocalemia, hipertensión, insuficiencia cardíaca congestiva, fibrilación auricular, o insuficiencia renal. Esta actividad de inhibición de la sintasa de aldosterona es fácilmente determinada por los expertos en la materia de acuerdo con los ensayos convencionales (por ejemplo, Patente de los Estados Unidos de Norteamérica Número US 2007/0049616).

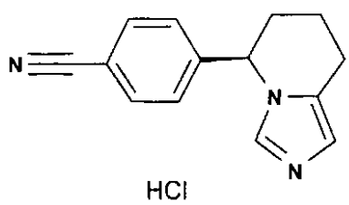
La clase de inhibidores de sintasa de aldosterona comprende

los inhibidores de sintasa de aldosterona tanto esteroideos como no esteroideos, prefiriéndose más los últimos.

Se da preferencia a los inhibidores de sintasa de aldosterona comercialmente disponibles, o a los inhibidores de sintasa de aldosterona que han sido aprobados por las autoridades de salud.

La clase de inhibidores de sintasa de aldosterona comprende compuestos que tienen diferentes características estructurales. Por ejemplo, se puede hacer mención de los compuestos que se seleccionan a partir del grupo que consiste en los inhibidores de aromatasa no esteroideos anastrozol, fadrozol (incluyendo el enantiómero (+) de los mismos), así como el inhibidor de aromatasa esteroideo exemestano, o, en cada caso cuando sea aplicable, una sal farmacéuticamente aceptable del mismo.

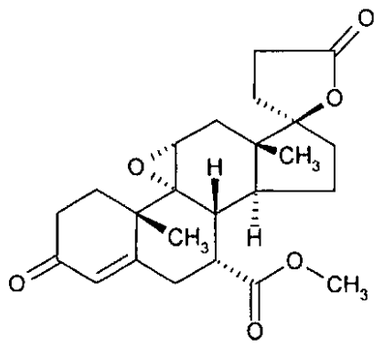
El inhibidor de sintasa de aldosterona no esteroideo más preferido es el enantiómero (+) del clorhidrato de fadrozol (Patentes de los Estados Unidos de Norteamérica Números 4617307 y 4889861) de la fórmula:



o, si es apropiado, una sal farmacéuticamente aceptable del mismo.

Un antagonista de aldosterona esteroideo preferido es

eplerenona (véase la Patente Europea Número EP 122232 A) de la fórmula:



o espironolactona; o, en cada caso, si es apropiado, una sal farmacéuticamente aceptable de la misma.

Los inhibidores de sintasa de aldosterona útiles en esta combinación son los compuestos y análogos genérica y específicamente dados a conocer, por ejemplo, en la Patente de los Estados Unidos de Norteamérica Número US2007/0049616, en particular en las reivindicaciones de los compuestos; y los productos finales de los ejemplos de procesamiento, el asunto objeto de los productos finales, las preparaciones farmacéuticas y las reivindicaciones se incorporan a la presente solicitud por referencia a esta publicación. Los inhibidores de sintasa de aldosterona preferidos adecuados para utilizarse en la presente invención incluyen, sin limitación, 4-(6,7-dihidro-5*H*-pirrolo-[1,2-*c*]-imidazol-5-il)-3-metil-benzonitrilo; (4-metoxi-bencil)-metil-amida del ácido 5-(2-cloro-4-ciano-fenil)-6,7-dihidro-5H-pirrolo-[1,2-c]-imidazol-5-carboxílico; 4'-fluoro-6-(6,7,8,9-tetrahidro-5*H*-imidazo-[1,5-*a*]-azepin-5-il)-bifenil-3-carbonitrilo; butil-éster del ácido 5-(4-ciano-2-metoxi-

fenil)-6,7-dihidro-5H-pirrolo-[1,2-c]-imidazol-5-carboxílico; 4-(6,7-dihidro-5H-pirrolo-[1,2-*c*]-imidazol-5-il)-2-metoxi-benzonitrilo; 4-fluoro-bencil-éster del ácido 5-(2-cloro-4-ciano-fenil)-6,7-dihidro-5*H*-pirrolo-[1,2-*c*]-imidazol-5-carboxílico; metil-éster del ácido 5-(4-ciano-2-trifluoro-metoxi-fenil)-6,7-dihidro-5H-pirrolo-[1,2-c]-imidazol-5-carboxílico; 2-isopropoxi-etil-éster del ácido 5-(4-ciano-2-metoxi-fenil)-6,7-dihidro-5*H*-pirrolo-[1,2-*c*]-imidazol-5-carboxílico; 4-(6,7-dihidro-5H-pirrolo-[1,2-*c*]-imidazol-5-il)-2-metil-benzonitrilo; 4-(6,7-dihidro-5*H*-pirrolo-[1,2-*c*]-imidazol-5-il)-3-fluoro-benzonitrilo; 4-(6,7-dihidro-5H-pirrolo-[1,2-*c*]-imidazol-5-il)-2-metoxi-benzonitrilo; 3-fluoro-4-(7-metilen-6,7-dihidro-5*H*-pirrolo-[1,2-*c*]-imidazol-5-il)-benzonitrilo; *cis*-3-fluoro-4-[7-(4-fluoro-bencil)-5,6,7,8-tetrahidro-imidazo-[1,5-a]-piridin-5-il]-benzonitrilo; 4'-fluoro-6-(9-metil-6,7,8,9-tetrahidro-5*H*-imidazo-[1,5-*a*]-azepin-5-il)-bifenil-3-carbonitrilo; 4'-fluoro-6-(9-metil-6,7,8,9-tetrahidro-5*H*-imidazo-[1,5-*a*]-azepin-5-il)-bifenil-3-carbonitrilo, o en cada caso, el enantiómero (R) o (S) de los mismos; o si es apropiado, una sal farmacéuticamente aceptable de los mismos.

El término "inhibidores de sintasa de aldosterona" también incluye los compuestos y análogos que se dan a conocer en las Publicaciones Internacionales Números WO2008/076860, WO2008/076336, WO2008/076862, WO2008/027284, WO2004/046145, WO2004/014914, y WO2001/076574.

Adicionalmente, los inhibidores de sintasa de aldosterona también incluyen los compuestos y análogos que se dan a conocer

en las Solicitudes de Patente de los Estados Unidos de Norteamérica Números US2007/0225232, US2007/0208035, US2008/0318978, US2008/0076794, US2009/0012068, US20090048241 y en las Solicitudes del TCP Números WO2006/005726, WO2006/128853, WO2006128851, WO2006/128852, WO2007065942, WO2007/116099, WO2007/116908, WO2008/119744, y en la Solicitud de Patente Europea Número EP 1886695. Los inhibidores de sintasa de aldosterona preferidos adecuados para utilizarse en la presente invención incluyen, sin limitación, 8-(4-fluoro-fenil)-5,6-dihidro-8H-imidazo-[5,1-c][1,4]-oxazina; 4-(5,6-dihidro-8H-imidazo-[5,1-c][1,4]-oxazin-8-il)-2-fluoro-benzonitrilo; 4-(5,6-dihidro-8H-imidazo-[5,1-c][1,4]-oxazin-8-il)-2,6-difluoro-benzonitrilo; 4-(5,6-dihidro-8H-imidazo-[5,1-c][1,4]-oxazin-8-il)-2-metoxi-benzonitrilo; 3-(5,6-dihidro-8H-imidazo-[5,1-c][1,4]-oxazin-8-il)-benzonitrilo; 4-(5,6-dihidro-8H-imidazo-[5,1-c][1,4]-oxazin-8-il)-ftalonitrilo; 4-(8-(4-ciano-fenil)-5,6-dihidro-8H-imidazo-[5,1-c][1,4]-oxazin-8-il)-benzonitrilo; 4-(5,6-dihidro-8H-imidazo-[5,1-c][1,4]-oxazin-8-il)-benzonitrilo; 4-(5,6-dihidro-8H-imidazo-[5,1-c][1,4]-oxazin-8-il)-naftalen-1-carbonitrilo; 8-[4-(1H-tetrazol-5-il)-fenil1-5,6-dihidro-8H-imidazo-[5,1-c][1,4]-oxazina, como es desarrollado por Speedel, o en cada caso, el enantiómero (R) o (S) de los mismos; o si es apropiado, una sal farmacéuticamente aceptable de los mismos.

El término "bloqueador de los receptores de endotelina" incluye bosentan, etc.

El término "inhibidor de CETP" se refiere a un compuesto que

inhibe el transporte mediado por la proteína de transferencia de colesteril-éster (CETP), de diferentes colesteril-ésteres y triglicéridos desde HDL hasta LDL y VLDL. Esta actividad de inhibición de la proteína de transferencia de colesteril-éster es fácilmente determinada por los expertos en este campo, de acuerdo con los ensayos convencionales (por ejemplo, la Patente de los Estados Unidos de Norteamérica Número 6,140,343). Los ejemplos incluyen los compuestos que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número 6,140,343 y en la Patente de los Estados Unidos de Norteamérica Número 6,197,786. (por ejemplo, etil-éster del ácido [2R,4S]4-[(3,5-bis-trifluoro-metil-bencil)-metoxi-carbonil-amino]-2-etil-6-trifluoro-metil-3,4-dihidro-2H-quinolin-1-carboxílico (torcetrapib); los compuestos que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número 6,723,752, (por ejemplo, (2R)-3-{[3-(4-cloro-3-etil-fenoxi)-fenil]-[[3-(1,1,2,2-tetrafluoro-etoxi)-fenil]-metil]-amino}-1,1,1-trifluoro-2-propanol); los compuestos que se dan a conocer en la Solicitud de Patente de los Estados Unidos de Norteamérica con Número de Serie 10/807,838; los derivados de polipéptido que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número 5,512,548; los derivados de rosenonolactona y los análogos de colesteril-éster que contienen fosfato que se dan a conocer en *J. Antibiot.,* 49(8): 815-816 (1996), y en *Bioorg. Med. Chem. Lett.;* 6: 1951-1954 (1996), respectivamente. Adicionalmente, los inhibidores de la proteína de transferencia de colesteril-éster (CETP) también incluyen aquéllos

que se dan a conocer en las Publicaciones Internacionales Números WO2000/017165, WO2005/095409 y WO2005/097806.

Un inhibidor de PDE5 preferido es Sildenafil.

Los segundos agentes de un interés particular incluyen antagonistas de endotelina, inhibidores de renina, antagonistas de los receptores de angiotensina II, bloqueadores del canal de calcio, diuréticos, agentes anti-diabéticos, tales como inhibidores de DPPIV, e inhibidores de sintasa de aldosterona.

EJEMPLIFICACIÓN DE LA INVENCIÓN:

Todos los materiales de partida, bloques de construcción, reactivos, ácidos, bases, agentes deshidratantes, solventes, y catalizadores utilizados para sintetizar los compuestos de la presente invención son cualquiera de los que se encuentran comercialmente disponibles, o se pueden producir mediante los métodos de síntesis orgánica conocidos por un experto ordinario en este campo (Houben-Weil, 4ª Edición 1952, Methods of Organic Synthesis, Thieme, Volumen 21). Además, los compuestos de la presente invención se pueden producir mediante los métodos de síntesis orgánica conocidos por un experto ordinario en este campo, como se muestra en los siguientes ejemplos.

Los siguientes ejemplos pretenden ilustrar la invención y no se deben interpretar como limitaciones sobre la misma. Las temperaturas se dan en grados centígrados. Si no se menciona de otra manera, todas las evaporaciones se llevan a cabo bajo presión reducida, de preferencia entre aproximadamente 15 mm Hg y 100 mm

Hg (= 20-133 mbar). La estructura de los productos finales, de los intermediarios, y de los materiales de partida se confirma mediante los métodos analíticos convencionales, por ejemplo, microanálisis y características espectroscópicas, por ejemplo, MS, IR, RMN. Las abreviaturas empleadas son las convencionales en este campo. Se ha encontrado que los compuestos de los Ejemplos 5-1 a 15-3 tienen valores IC_{50} en el intervalo de aproximadamente 0.01 nM a aproximadamente 10,000 nM para la endopeptidasa neutra (NEP).

Las condiciones para medir los tiempos de retención son como sigue:

HPLC - condición A:

Columna: INERTSIL C8-3, 3 micras x 33 milímetros x 3.0 milímetros a 40°C.

Velocidad de flujo: 2 mililitros / minuto.

Fase móvil: A) $HCOONH_4$ acuoso 5 mM, B) metanol / CH_3CN (1 / 1, volumen / volumen).

Gradiente: gradiente lineal desde el 5 por ciento de A hasta el 95 por ciento de B en 2 minutos.

Detección: DAD-UV a 200-400 nanómetros.

HPLC - condición B:

Columna: INERTSIL C8-3, 3 micras x 33 milímetros x 3.0 milímetros a 40°C.

Velocidad de flujo: 2 mililitros / minuto.

Fase móvil: A) $HCOONH_4$ acuoso 5 mM, B) metanol / CH_3CN (1 / 1, volumen / volumen).

Gradiente: gradiente lineal desde el 40 por ciento de A hasta el 95 por ciento de B en 2 minutos.

Detección: DAD-UV a 200-400 nanómetros.

HPLC - condición C:

Columna: INERTSIL C8-3, 3 micras x 33 milímetros x 3.0 milímetros a 40°C.

Velocidad de flujo: 2 mililitros / minuto.

Fase móvil: A) ($NH_4^+HCOO^-$ 5 mM)/agua, B) metanol / CH_3CN (1 / 1, volumen / volumen).

Gradiente: gradiente lineal desde el 5 hasta el 95 por ciento de B en 2 minutos.

Detección: DAD-UV a 200-400 nanómetros.

HPLC - condición D:

Columna: INERTSIL C8-3, 3 micras x 33 milímetros x 3.0 milímetros a 40°C.

Velocidad de flujo: 2 mililitros / minuto.

Fase móvil: A) ácido fórmico acuoso al 0.1 por ciento, B) metanol / CH_3CN (1 / 1, volumen / volumen).

Gradiente: gradiente lineal desde el 5 por ciento de B hasta el 95 por ciento de B en 2 minutos.

Detección: DAD-UV a 200-400 nanómetros.

HPLC - condición E:

Columna: Inertsil C8-3, 3 micras x 33 milímetros x 3.0 milímetros a 40°C.

Velocidad de flujo: 2 mililitros / minuto.

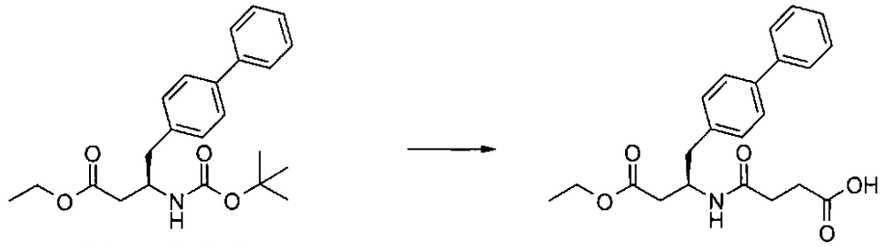
Fase móvil: A) metanol / acetonitrilo (1 / 1, volumen / volumen), B) $HCOONH_4$ acuoso 5 mM.

Gradiente: gradiente lineal desde el 40 por ciento de B hasta el 95 por ciento de A en 2 minutos.

Detección: UV a 214 nanómetros.

La estereoquímica relativa se determinó utilizando RMN bidimensional. Bajo las condiciones de reacción, sería inesperado que se racemizara el estereocentro que lleva el grupo bis-fenil-metilo. Por consiguiente, la estereoquímica absoluta se determinó basándose en la estereoquímica relativa y en la estereoquímica absoluta del estereocentro que lleva el grupo bis-fenil-metilo.

Ejemplo 1-1: Síntesis de ácido (R)-4-(1-(bifenil-4-il)-4-etoxi-4-oxobutan-2-il-amino)-4-oxo-butanoico

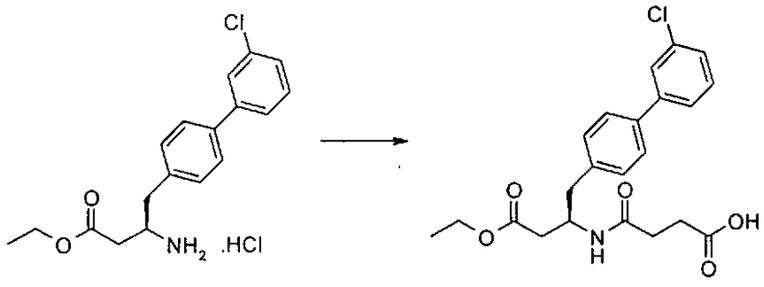


Intermediario 2

Al 4-(bifenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-etilo (230.1 miligramos, 0.600 milimoles), se le agrega una solución de HCl en 1,4-dioxano (3.00 mililitros, 12.00 milimoles) a temperatura ambiente. Después de agitar durante 1 hora, la mezcla de reacción se concentra bajo presión reducida, para dar el clorhidrato de etil-éster del ácido (R)-3-amino-4-bifenil-4-il-butírico. Una solución de clorhidrato de etil-éster del ácido (R)-3-amino-4-

bifenil-4-il-butírico, anhídrido succínico (72.1 miligramos, 0.720 milimoles), y di-isopropil-etil-amina (0.126 mililitros, 0.720 milimoles) en dicloro-metano (4 mililitros) se deja agitándose durante 1 hora. La reacción se apaga con ácido cítrico acuoso al 10 por ciento, y se extrae con dicloro-metano. La capa orgánica se separa y se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea sobre gel de sílice modificado por CN (eluyente: heptano/EtOAc = 100:0 a 0:100), y mediante HPLC en fase inversa (SunFire C18, H_2O (ácido trifluoro-acético al 0.1 por ciento)/CH_3CN), para dar el ácido (R)-4-(1-(bifenil-4-il)-4-etoxi-4-oxobutan-2-il-amino)-4-oxo-butanoico (148.2 mili-gramos). HPLC - tiempo de retención = 1.64 minutos (condición A); MS (m+1) = 384.1; ^{1}H RMN (400 MHz, ACETONITRILO-*d*3) δ ppm 1.21 (t, *J*=7.07 Hz, 3 H) 2.31 - 2.39 (m, 2 H) 2.40 - 2.56 (m, 4 H) 2.77 - 2.92 (m, 2 H) 4.08 (q, *J*=7.24 Hz, 2 H) 4.33 - 4.48 (m, 1 H) 6.62 (d, *J*=8.34 Hz, 1 H) 7.30 (d, *J*=8.08 Hz, 2 H) 7.32 - 7.39 (m, 1 H) 7.41 - 7.49 (m, 2 H) 7.54 - 7.60 (m, 2H) 7.60 - 7.67 (m, 2 H) 10.02 (br. s., 1 H).

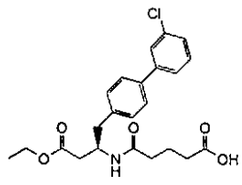
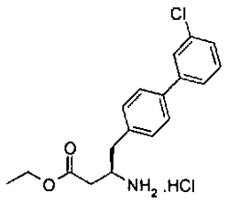
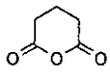
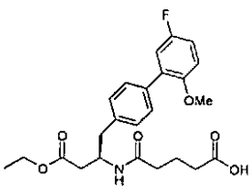
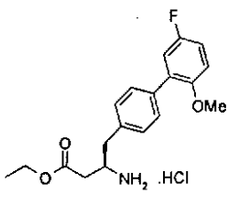
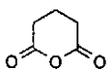
Ejemplo 1-2: Síntesis de ácido (R)-4-(1-(3'-cloro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico

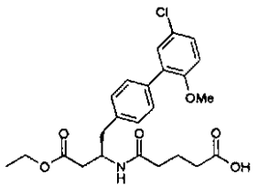
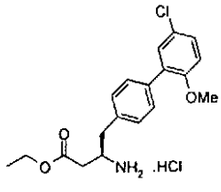
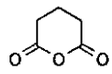
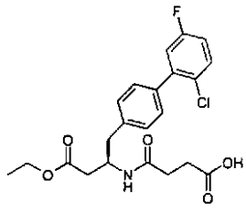
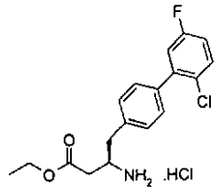
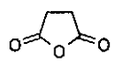


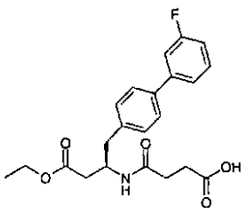
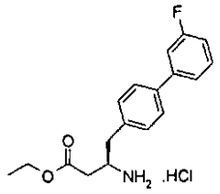
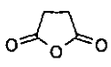
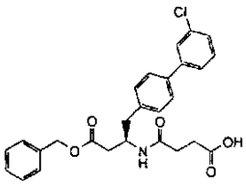
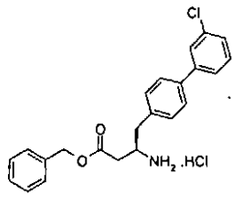
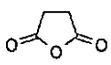
Una solución de clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-etilo (400 miligramos, 1.13 milimoles), anhídrido succínico (136 miligramos, 1.36 milimoles), y di-isopropil-etil-amina (0.237 mililitros, 1.36 milimoles) en dicloro-metano (5 mililitros) se deja agitándose durante 2.5 horas. La reacción se apaga con HCl acuoso 1 M, y se extrae con dicloro-metano. La capa orgánica se separa y se concentra bajo presión reducida. El residuo resultante se purifica mediante HPLC de preparación utilizando un gradiente del 20 por ciento de MeCN/agua (ácido trifluoro-acético al 0.1 por ciento) al 100 por ciento de MeCN, para dar el ácido (R)-4-(1-(3'-cloro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico (255 miligramos). HPLC - tiempo de retención = 1.15 minutos (condición B); MS (m+1) = 418.0; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J* = 7.08 Hz, 3 H) 2.46 - 2.58 (m, 4 H) 2.64 – 2.67 (m, 2 H) 2.87 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.99 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.6 Hz, 1 H) 4.12 – 4.24 (m, 2 H) 4.47 - 4.55 (m, 1 H) 6.50 (br d, *J* = 8.8 Hz, 1 H) 7.24 - 7.37 (m, 4 H) 7.43 - 7.46 (m, 1 H) 7.48 - 7.52 (m, 2H) 7.55 – 7.56 (m, 1 H).

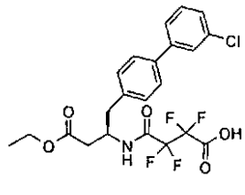
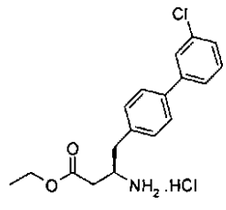
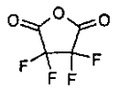
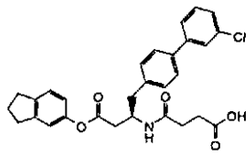
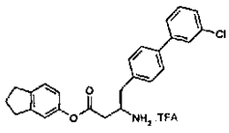
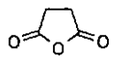
HPLC quiral - tiempo de retención = 3.59 minutos. Columna: Daicel CHIRALPAK AD-H (4.6 x 100 milímetros); velocidad de flujo = 1 mililitro/minuto.; eluyente: EtOH (que contiene ácido trifluoro-acético al 0.1 por ciento)/heptano = 4/6.

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 1-2:

Ej. #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
Ejemplo 1-3	 ácido (R)-5-(1-(3'-cloro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-5-oxo-pentanoico		 DIPEA, DCM, RT	1.57 minutos. (A)	432.1
Ejemplo 1-4	 ácido (R)-5-(4-etoxi-1-(5'-fluoro-2'-metoxi-bifenil-4-il)-4-oxo-butan-2-il-amino)-5-oxo-pentanoico		 DIPEA, DCM, RT	0.93 minutos. (B)	446.3

Ej. #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
Ejemplo 1-5	 ácido (R)-5-(1-(5'-cloro-2'-metoxi-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-5-oxo-pentanoico		 DIPEA, DCM, RT	1.14 minutos. (B)	462.5
Ejemplo 1-6	 ácido (R)-4-(1-(2''-cloro-5'-fluoro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-		 DIPEA, DCM, RT	0.97 minutos. (B)	436.2

Ej. #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
	butanoico				
Ejemplo 1-7	 ácido (R)-4-(4-etoxi-1-(3'-fluoro-bifenil-4-il)-4-oxo-butan-2-il-amino)-4-oxo-butanoico		 DIPEA, DCM, RT	1.23 minutos. (B)	402.0
Ejemplo 1-8	 ácido (R)-4-(4-(benciloxi)-1-(3'-cloro-bifenil-4-il)-4-oxo-		 DIPEA, DCM, RT	1.37 minutos. (B)	480.2

Ej. #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
	butan-2-il-amino)-4-oxo-butanoico				
Ejemplo 1-9			 Piridina, RT	1.32 minutos. (C)	490.2
Ejemplo 1-10			 DIPEA, DCM, RT	1.52 minutos. (B)	506.4

Ejemplo 1-3: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J* = 7.2 Hz, 3 H) 1.86 - 1.97 (m, 2 H) 2.25 - 2.28 (m, 2 H) 2.34 (t, *J* = 7.0 Hz, 2 H) 2.50 (A de ABX, J_{ab} = 16.2 Hz, Jax = 5.6 Hz, 1 H) 2.56 (B de ABX, J_{ab} = 16.2 Hz, J_{bx} = 5.1 Hz, 1 H) 2.88 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.98 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 7.1 Hz, 1 H) 4.12 - 4.23 (m, 2 H) 4.50 - 4.58 (m, 1 H) 6.32 (br d, *J* = 8.8 Hz, 1 H) 7.25 - 7.37 (m, 4 H) 7.43 - 7.46 (m, 1 H) 7.49 - 7.52 (m, 2 H) 7.55 - 7.56 (m, 1 H).

Ejemplo 1-4: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.29 (t, J = 7.1 Hz, 3 H) 1.86 - 1.97 (m, 2 H) 2.25 - 2.28 (m, 2 H) 2.34 (t, J = 7.0 Hz, 2 H) 2.54 (A de ABX, J_{ab} = 16.1 Hz, J_{ax} = 5.6 Hz, 1 H) 2.58 (B de ABX, J_{ab} = 16.1 Hz, J_{bx} = 5.2 Hz, 1 H) 2.88 (A de ABX, J_{ab} = 13.5 Hz, J_{ax} = 7.6 Hz, 1 H) 2.97 (B de ABX, J_{ab} = 13.5 Hz, J_{bx} = 7.0 Hz, 1 H) 3.78 (s, 3 H) 4.12 - 4.23 (m, 2 H) 4.50 - 4.59 (m, 1 H) 6.34 (br d, J = 8.6 Hz, 1 H) 6.88 - 6.91 (m, 1 H) 6.96 - 7.04 (m, 2 H) 7.23 (d, J = 8.3 Hz, 2 H) 7.44 - 7.47 (m, 2 H).

Ejemplo 1-5: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.29 (t, J = 7.1 Hz, 3 H) 1.86 - 1.97 (m, 2 H) 2.25 - 2.36 (m, 4 H) 2.49 - 2.61 (m, 2 H) 2.88 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.6 Hz, 1 H) 2.97 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.8 Hz, 1 H) 3.79 (s, 3 H) 4.12 - 4.23 (m, 2 H) 4.50 - 4.59 (m, 1 H) 6.34 - 6.36 (m, 1 H) 6.89 (d, J = 8.6 Hz, 1 H) 7.21 - 7.28 (m, 3 H) 7.43 (d, J = 8.1 Hz, 2 H).

Ejemplo 1-6: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.29 (t, J = 7.1 Hz, 3 H) 2.47 - 2.67 (m, 6 H) 2.89 (A de ABX, J_{ab} = 13.7 Hz, J_{ax} = 7.8 Hz, 1 H) 3.00 (B de ABX, J_{ab} = 13.7 Hz, J_{bx} = 6.7 Hz, 1 H) 4.12 - 4.24 (m, 2 H) 4.49 - 4.57 (m, 1 H) 6.51 (br d, J = 8.6 Hz, 1 H) 6.97 - 7.07 (m, 2 H) 7.24 - 7.26 (m, 2 H) 7.36 - 7.43 (m, 3 H).

Ejemplo 1-7: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1.16 (t, J = 7.1 Hz, 3 H) 2.23 - 2.27 (m, 2 H) 2.34 - 2.38 (m, 2 H) 2.40 - 2.47 (m, 2 H) 2.77 (d, J = 6.6 Hz, 2 H) 3.99 - 4.06 (m, 2 H) 4.21 - 4.30 (m, 1 H) 7.14 - 7.19 (m, 1 H) 7.29 (d, J = 8.4 Hz, 2 H) 7.46 - 7.52 (m, 3 H) 7.63 (d, J = 8.4 Hz, 2 H) 7.91 (d, J = 8.3 Hz, 1 H) 12.04 (s, 1 H).

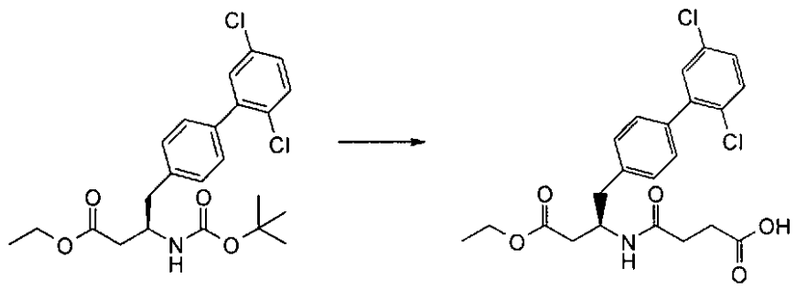
Ejemplo 1-8: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 2.41 -

2.45 (m, 2 H) 2.50 - 2.64 (m, 4 H) 2.81 - 2.87 (m, 1 H) 2.95 - 3.00 (m, 1 H) 4.49 – 4.56 (m, 1 H) 5.12 (A de AB, *J* = 12.1 Hz, 1 H) 5.18 (B de AB, *J* = 12.1 Hz, 1 H) 6.39 (d, *J* = 8.1 Hz, 1 H) 7.18 - 7.54 (m, 13 H).

Ejemplo 1-9: ^{1}H RMN (400 MHz, DMSO-d6): ^{1}H RMN (400 MHz, DMSO-d6): δ ppm 1.22-1.25 (t, J=7.07 Hz, 3H), 2.61-2.63 (m, 2H), 2.91 (d, J=7.07 Hz, 2H), 4.09 (q, J=7.07 Hz, 2H), 4.52-4.59 (m, 1H), 7.32-7.34 (m, 3H), 7.04 (t, J=7.83 Hz, 1H), 7.52-7.56 (m, 3H), 7.59 (t, J=2.02 Hz, 1H).

Ejemplo 1-10: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 2.03 - 2.13 (m, 2 H), 2.44 (t, J=6.3 Hz, 2 H), 2.64 (t, J=6.6 Hz, 2 H), 2.70 (dd, J=16.2, 5.6 Hz, 1 H), 2.78 (dd, J=16.2, 5.1 Hz, 1 H), 2.83 - 2.98 (m, 5 H), 3.04 (dd, J=13.9, 6.8 Hz, 1 H), 4.57 - 4.69 (m, 1 H), 6.51 (d, J=8.8 Hz, 1 H), 6.79 (dd, J=8.1, 2.3 Hz, 1 H), 6.90 (d, J=1.8 Hz, 1 H), 7.18 (d, J=8.1 Hz, 1 H), 7.26 - 7.31 (m, 3 H), 7.34 (t, J=7.7 Hz, 1 H), 7.43 (dt, J=7.3, 1.5 Hz, 1 H), 7.49 (d, J=8.1 Hz, 2 H), 7.54 (t, J=1.8 Hz, 1 H), 9.34 (br. s., 1 H).

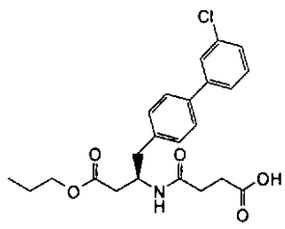
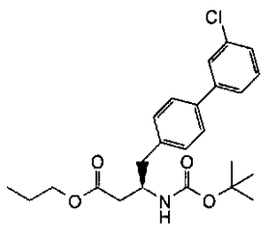
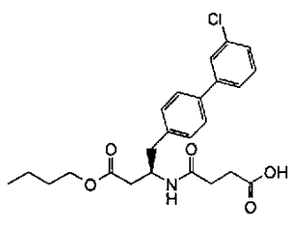
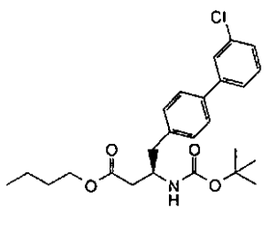
Ejemplo 1-11: Síntesis de ácido (R)-4-(1-(2',5'-dicloro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico

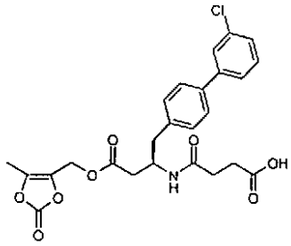
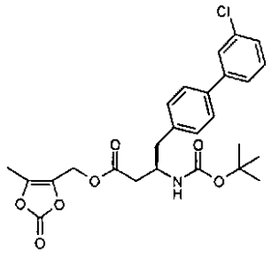
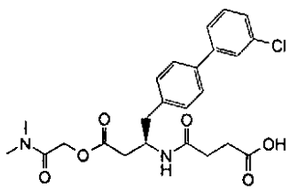
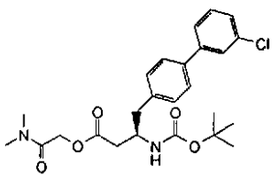


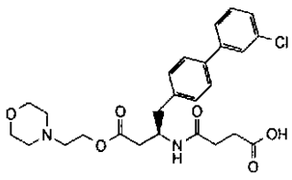
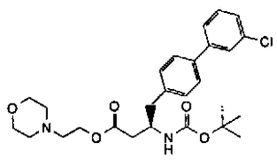
Al 3-(terbutoxi-carbonil-amino)-4-(2',5'-dicloro-bifenil-4-il)-butanoato de (R)-etilo (1.09 gramos, 2.33 milimoles), se le agrega

una solución de HCl 4M en 1,4-dioxano (5.81 mililitros, 23.3 milimoles) a temperatura ambiente. Después de agitar durante 2 horas, la mezcla de reacción se concentra bajo presión reducida, para dar clorhidrato de 3-amino-4-(2',5'-dicloro-bifenil-4-il)-butanoato de (R)-etilo. En seguida, una solución del producto, anhídrido succínico (280 miligramos, 2.80 milimoles), y di-isopropil-etil-amina (0.489 mililitros, 2.80 milimoles) en dicloro-metano (15 mililitros) se deja agitándose durante 2 horas. La reacción se apaga con HCl acuoso 1 M, y se extrae con dicloro-metano. La capa orgánica se separa y se concentra bajo presión reducida. El residuo resultante se purifica mediante HPLC de preparación utilizando un gradiente del 20 por ciento de MeCN/agua (ácido trifluoro-acético al 0.1 por ciento) al 100 por ciento de MeCN, para dar el ácido (R)-4-(1-(2',5'-dicloro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico (553 mili-gramos) como un sólido blanco; HPLC - tiempo de retención = 1.02 minutos (condición B); MS (m+1) = 452.14; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J* = 7.2 Hz, 3 H) 2.47 - 2.67 (m, 6 H) 2.89 (A de ABX, J_{ab} = 13.7 Hz, J_{ax} = 7.8 Hz, 1 H) 3.00 (B de ABX, J_{ab} = 13.7 Hz, J_{bx} = 6.7 Hz, 1 H) 4.12 - 4.24 (m, 2 H) 4.49 - 4.57 (m, 1 H) 6.53 (br d, *J* = 8.8 Hz, 1 H) 7.23 - 7.26 (m, 3 H) 7.32 - 7.40 (m, 4 H).

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 1-11:

Ejemplo	Producto	Material de Partida	HPLC-RT (condición)	MS (M+1)
Ejemplo 1-12	 propil-éster del ácido (R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-butírico		1.24 minutos. (B)	432.3
Ejemplo 1-13	 butil-éster del ácido (R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-butírico		1.34 minutos. (B)	446.2

Ejemplo	Producto	Material de Partida	HPLC-RT (condición)	MS (M+1)
Ejemplo 1-14	 5-metil-2-oxo-[1,3]-dioxol-4-il-metil-éster del ácido (R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-butírico		1.12 minutos. (B)	502.2
Ejemplo 1-15	 dimetil-carbamoil-metil-éster del ácido (R)-3-(3-carboxi-propionil-		0.89 minutos. (B)	475.3

Ejemplo	Producto	Material de Partida	HPLC-RT (condición)	MS (M+1)
	amino)-4-(3'-cloro-bifenil-4-il)-butírico			
Ejemplo 1-16	 2-morfolin-4-il-etil-éster del ácido (R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-butírico		0.99 minutos. (B)	503.5

Ejemplo 1-12: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 0.87 (t, J=7.5 Hz, 3 H), 1.49 - 1.61 (m, 2 H), 2.22 - 2.29 (m, 2 H), 2.32 - 2.39 (m, 2 H), 2.45 (dd, J=6.9, 3.4 Hz, 2 H), 2.78 (d, J=6.6 Hz, 2 H), 3.94 (t, J=6.6 Hz, 2 H), 4.21 - 4.33 (m, 1 H), 7.29 (d, J=8.3 Hz, 2 H), 7.37 - 7.42 (m, 1 H), 7.47 (t, J=7.8 Hz, 1 H), 7.58 - 7.65 (m, 3 H), 7.69 (t, J=1.9 Hz, 1 H), 7.92 (d, J=8.3 Hz, 1 H).

Ejemplo 1-13: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 0.94

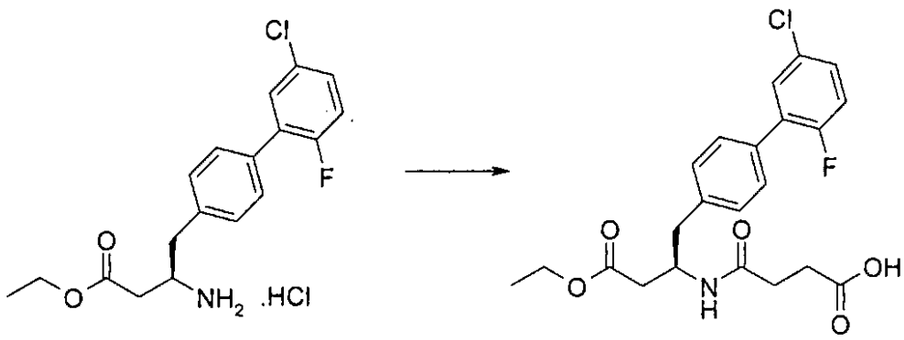
(t, J=7.3 Hz, 3 H), 1.32 - 1.44 (m, 2 H), 1.56 - 1.67 (m, 2 H), 2.43 - 2.59 (m, 4 H), 2.65 (t, J=6.4 Hz, 2 H), 2.85 (dd, J=13.6, 8.1 Hz, 1 H), 2.99 (dd, J=13.6, 6.6 Hz, 1 H), 4.03 - 4.18 (m, 2 H), 4.43 - 4.56 (m, 1 H), 6.57 (d, J=8.6 Hz, 1 H), 7.25 (d, J=8.3 Hz, 2 H), 7.28 - 7.32 (m, 1 H), 7.35 (t, J=7.7 Hz, 1 H), 7.41 - 7.46 (m, 1 H), 7.48 (d, J=8.1 Hz, 2 H), 7.55 (t, J=1.8 Hz, 1 H).

Ejemplo 1-14: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 2.17 (s, 3 H), 2.44 (t, J=6.2 Hz, 2 H), 2.48 - 2.57 (m, 1 H), 2.57 - 2.73 (m, 3 H), 2.87 (dd, J=13.6, 7.6 Hz, 1 H), 2.98 (dd, J=13.9, 7.1 Hz, 1 H), 4.47 - 4.58 (m, 1 H), 4.84 (s, 2 H), 6.32 (d, J=8.6 Hz, 1 H), 7.23 (d, J=8.1 Hz, 2 H), 7.30 (d, 1 H), 7.35 (t, J=7.7 Hz, 1 H), 7.44 (d, J=7.3 Hz, 1 H), 7.49 (d, J=8.1 Hz, 2 H), 7.54 (s, 1 H).

Ejemplo 1-15: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 2.48 - 2.59 (m, 3 H), 2.61 - 2.71 (m, 3 H), 2.91 - 3.06 (m, 8 H), 4.53 - 4.63 (m, 1 H), 4.67 (d, J=14.7 Hz, 1 H), 5.03 (d, J=14.7 Hz, 1 H), 7.30 (dt, J=7.8, 1.8 Hz, 1 H), 7.32 - 7.38 (m, 3 H), 7.45 (dt, J=7.6, 1.5 Hz, 1 H), 7.50 (d, J=8.1 Hz, 2 H), 7.55 (t, J=1.8 Hz, 1 H), 8.08 (d, J=9.3 Hz, 1 H).

Ejemplo 1-16: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.20 - 2.32 (m, 2 H), 2.32 - 2.41 (m, 2 H), 2.42 - 2.50 (m, 1 H), 2.57 (dd, J=15.4, 5.6 Hz, 1 H), 2.80 (d, J=36.1 Hz, 2 H), 3.15 (br. s., 2 H), 3.31 - 3.50 (m, 4 H), 3.52 - 4.05 (m, 4 H), 4.25 - 4.40 (m, 3 H), 7.31 (d, J=8.3 Hz, 2 H), 7.39 - 7.43 (m, 1 H), 7.48 (t, J=7.8 Hz, 1 H), 7.60 - 7.67 (m, 3 H), 7.70 (t, J=1.8 Hz, 1 H), 8.02 (d, J=8.6 Hz, 1 H), 10.06 (br. s., 1 H), 12.17 (br. s., 1 H).

Ejemplo 1-17: Síntesis de ácido (R)-4-(1-(5'-cloro-2'-fluoro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico

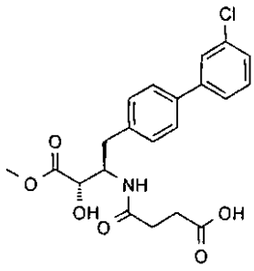
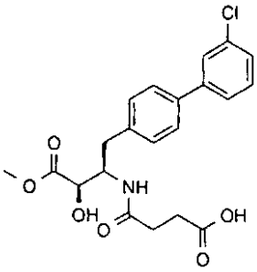
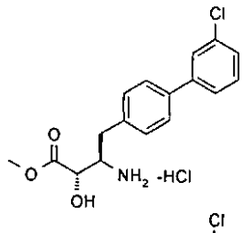
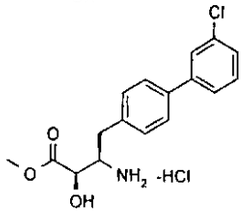
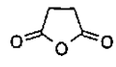


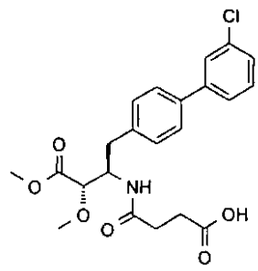
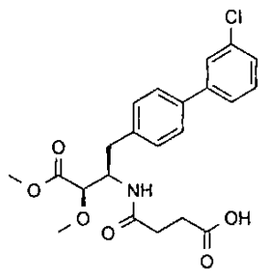
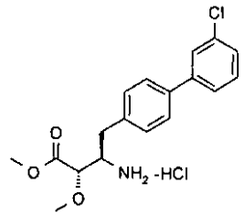
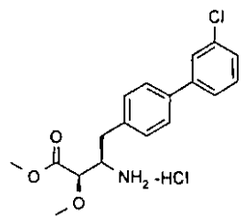
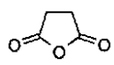
Una solución de clorhidrato de 3-amino-4-(5'-cloro-2'-fluoro-bifenil-4-il)-butanoato de (R)-etilo (293 miligramos, 0.777 milimoles), anhídrido succínico (93 miligramos, 0.932 milimoles), y di-isopropil-etil-amina (0.204 mililitros, 1.165 milimoles) en dicloro-metano (4 mililitros) se deja agitándose durante 1.5 horas. La reacción se apaga con HCl acuoso 1 M, y se extrae con dicloro-metano. La capa orgánica se separa y se concentra bajo presión reducida. El residuo resultante se purifica mediante HPLC de preparación utilizando un gradiente del 20 por ciento de MeCN/agua (ácido trifluoro-acético al 0.1 por ciento) al 100 por ciento de MeCN, para dar el ácido (R)-4-(1-(5'-cloro-2'-fluoro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico (294 miligramos). HPLC - tiempo de retención = 1.03 minutos (condición B); MS (m+1) = 436.2; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, *J* = 7.07 Hz, 3 H) 2.46 - 2.58 (m, 4 H) 2.64 – 2.68 (m, 2 H) 2.87 (A de ABX, J_{ab} = 13.64 Hz, J_{ax} = 7.83 Hz, 1 H) 2.99 (B de ABX, J_{ab} = 13.64 Hz, J_{bx} = 6.57 Hz, 1 H) 4.11 – 4.22 (m, 2 H) 4.47 - 4.56 (m, 1 H) 6.60 (br d, *J* = 8.59 Hz, 1 H) 7.05 –

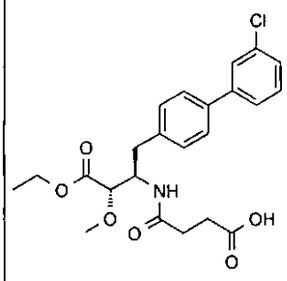
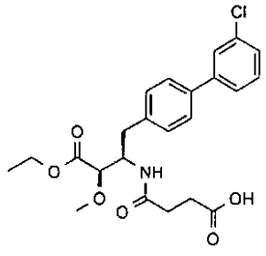
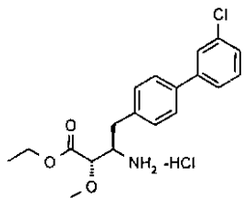
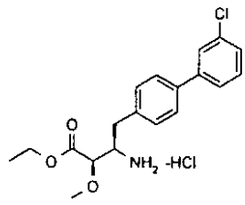
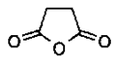
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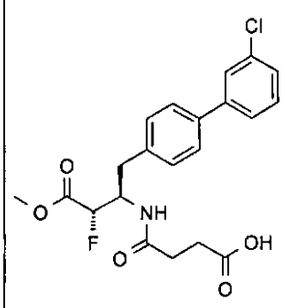
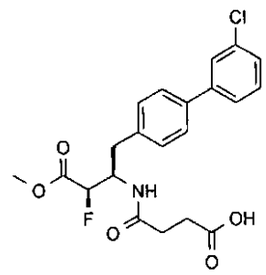
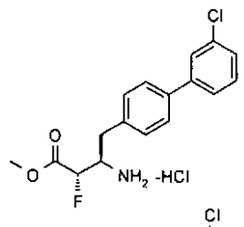
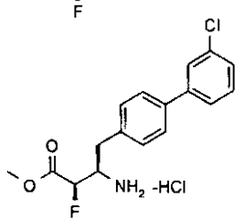
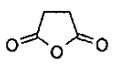
7.10 (m, 1 H) 7.23 - 7.27 (m, 3 H) 7.39 - 7.41 (m, 1 H) 7.44 - 7.46 (m, 2H).

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 1-17:

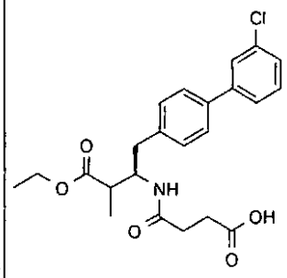
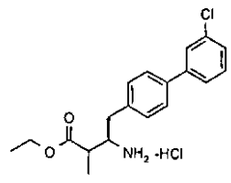
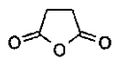
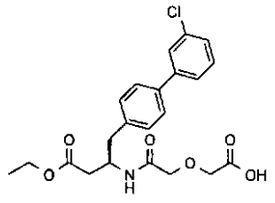
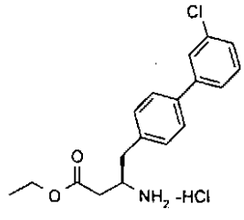
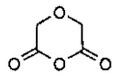
Ejemplo #	Producto	Material de Partida	Condición	HPLC-RT (condición)	MS (M+1)
Ejemplo 1-18	 metil-éster del ácido (2S,3R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-hidroxi-butírico  metil-éster del ácido (2R,3R)-3-(3-	  Intermediario 50	 Et_3N, DCM	1.29 minutos. (A)	420.0

Ejemplo #	Producto	Material de Partida	Condición	HPLC-RT (condición)	MS (M+1)
	carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-hidroxi-butírico				
Ejemplo 1-19	 metil-éster del ácido (2S,3R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-metoxi-butírico  metil-éster del ácido (2R,3R)-3-(3-	  Intermediario 51	 DIPEA, DCM	1.21 minutos. (A)	434.2

Ejemplo #	Producto	Material de Partida	Condición	HPLC-RT (condición)	MS (M+1)
	carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-metoxi-butírico				
Ejemplo 1-20	 etil-éster del ácido (2S,3R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-metoxi-butírico  etil-éster del ácido (2R,3R)-3-(3-	  Intermediario 52	 DIPEA, DCM	1.57 minutos. (A)	448.3

Ejemplo #	Producto	Material de Partida	Condición	HPLC-RT (condición)	MS (M+1)
	carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-metoxi-butírico				
Ejemplo 1-21	 metil-éster del ácido (2S,3R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-fluoro-butírico  metil-éster del	  Intermediario 53	 Et_3N, DCM	0.83 minutos. (B)	422.1

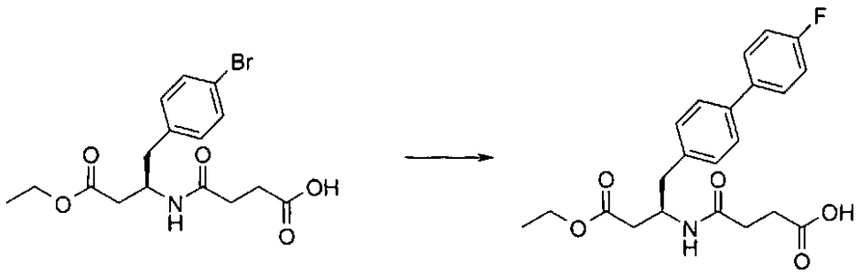
915

Ejemplo #	Producto	Material de Partida	Condición	HPLC-RT (condición)	MS (M+1)
	ácido (2R,3R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-fluoro-butírico				
Ejemplo 1-22	 etil-éster del ácido (R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-metil-butírico	 Nuevo intermediario 54	 Et_3N, DCM	0.98 minutos. (B)	432
Ejemplo 1-23	 etil-éster del ácido (R)-3-(2-carboxi-		 Et_3N, DCM	0.75 minutos. (B)	434

Ejemplo #	Producto	Material de Partida	Condi-ción	HPLC-RT (condición)	MS (M+1)
	metoxi-acetil-amino)-4-(3'-cloro-bifenil-4-il)-butírico				

Ejemplo 1-20: ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.15 (t, *J* = 7.07 Hz, 3 H), 2.24-2.34 (m, 4 H), 2.74 (dd, *J* = 8.59, 13.39 Hz), 2.88 (dd, *J* = 6.32, 13.39 Hz), 3.34 (s, 3H), 3.75 (d, *J* = 2.78 Hz, 1 H), 4.04 (dd, *J* = 7.07, 13.89 Hz, 2 H), 4.33-4.43 (m, 1 H), 7.31 (d, *J* = 8.08 Hz, 2 H), 7.38-7.43 (m, 1 H), 7.48 (t, *J* = 7.83 Hz, 1 H), 7.63 (d, *J* = 3.34 Hz), 7.71 (t, *J* = 1.77 Hz, 1 H), 7.95 (d, *J* = 9.35 Hz, 1 H).

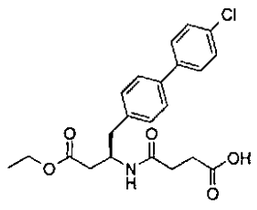
Ejemplo 2-1: Síntesis de etil-éster del ácido (R)-3-(3-carboxi-propionil-amino)-4-(4'-fluoro-bifenil-4-il)-butírico

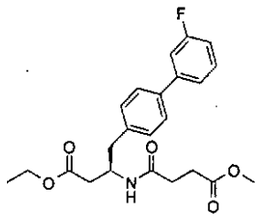
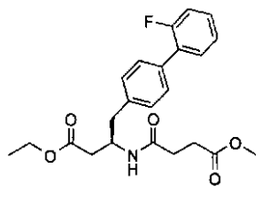


Una mezcla del ácido (R)-4-(1-(4-bromo-fenil)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico (50 miligramos, 0.129 milimoles), ácido 4-fluoro-fenil-borónico (27.2 miligramos, 0.194 milimoles), $Pd(Ph_3P)_4$ (14.96 miligramos, 0.013 milimoles), y Na_2CO_3 acuoso (0.129 mililitros, 0.259 milimoles) en tolueno (1 mililitro) se deja

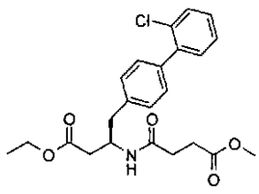
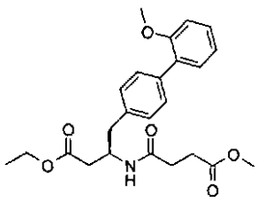
agitándose a 95°C bajo nitrógeno. Después de agitar durante 13 horas, la solución se enfría a temperatura ambiente, y entonces se apaga con HCl acuoso 1M. Los productos se extraen con acetato de etilo, se lavan con salmuera, se secan sobre $MgSO_4$, se filtran, y se concentran bajo presión reducida. El residuo obtenido se purifica mediante HPLC de fase inversa (SunFire C18, H_2O (ácido trifluoro-acético al 0.1 por ciento)/CH_3CN), y se liofiliza, para dar el etil-éster del ácido (R)-3-(3-carboxi-propionil-amino)-4-(4'-fluoro-bifenil-4-il)-butírico (29.2 miligramos). HPLC - tiempo de retención = 1.26 minutos (condición B); MS (m+1) = 402.2; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, J = 7 Hz, 3 H) 2.47 – 2.67 (m, 6 H) 2.87 (A de ABX, Jab = 13.7 Hz, Jax = 7.9 Hz, 1 H) 2.99 (B de ABX, Jab = 13.7 Hz, Jbx = 6.6 Hz, 1 H) 4.12 – 4.23 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.52 (br d, J = 8.6 Hz, 1 H) 7.08 – 7.14 (m, 2 H) 7.24 (d, J = 8.4 Hz, 2 H) 7.46 – 7.55 (m, 4 H).

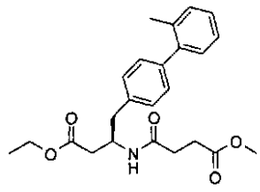
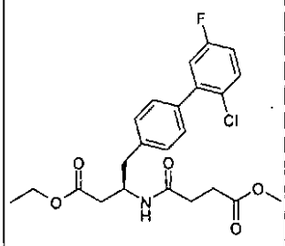
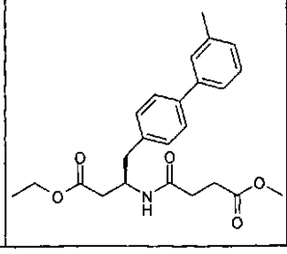
Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 2-1:

Ejemplo	**Producto**	**Reactivo**	**HPLC-RT (condición)**	**MS (M+1)**
Ejemplo 2-2		$Pd(PPh_3)_4$, ácido p-cloro-fenil-borónico, Na_2CO_3 acuoso 2M, ácido (R)-4-(1-(4-bromo-fenil)-	1.49 minutos. (B)	418.1

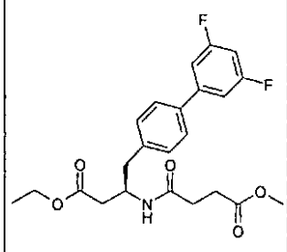
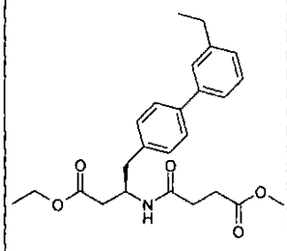
Ejemplo	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
		4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico		
Ejemplo 2-3		$Pd(PPh_3)_4$, ácido *m*-fluoro-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.24 minutos. (B)	416.1
Ejemplo 2-4		$Pd(PPh_3)_4$, ácido *o*-fluoro-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.25 minutos. (B)	416.1

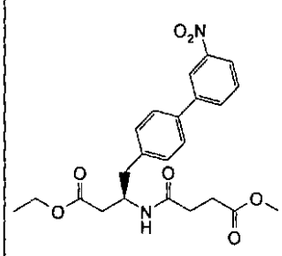
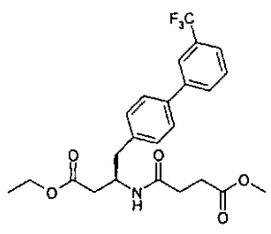
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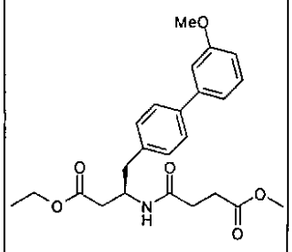
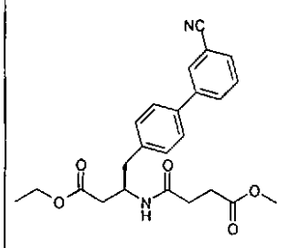
Ejemplo	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
Ejemplo 2-5		$Pd(PPh_3)_4$, ácido o-cloro-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.33 minutos. (B)	432.1
Ejemplo 2-6		$Pd(PPh_3)_4$, ácido *o*-metoxi-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.22 minutos. (B)	428.2

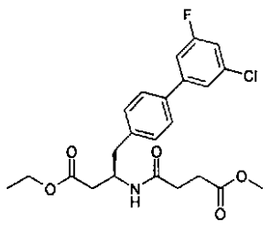
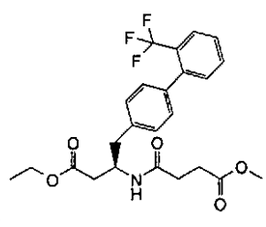
Ejemplo	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
Ejemplo 2-7		$Pd(PPh_3)_4$, ácido *o*-tolil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.35 minutos. (B)	412.2
Ejemplo 2-8		$Pd(PPh_3)_4$, ácido 2-cloro-5-fluoro-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.28 minutos. (B)	450.3
Ejemplo 2-9		$Pd(PPh_3)_4$, ácido m-tolil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-	1.28 minutos. (B)	412.2

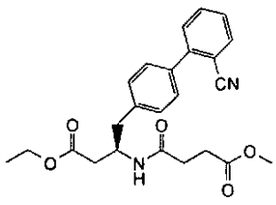
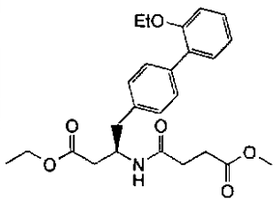
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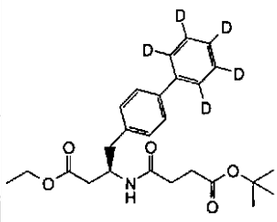
Ejemplo	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
		(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.		
Ejemplo 2-10		$Pd(PPh_3)_4$, ácido 3,5-difluoro-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.23 minutos. (B)	434.2
Ejemplo 2-11		$Pd(PPh_3)_4$, ácido 3-etil-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-	1.40 minutos. (B)	426.3

Ejemplo	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
		etilo.		
Ejemplo 2-12		$Pd(PPh_3)_4$, ácido 3-nitro-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.16 minutos. (B)	443.2
Ejemplo 2-13		$Pd(PPh_3)_4$, ácido 3-(trifluoro-metil)-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.39 minutos. (G)	466.1

Ejemplo	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
Ejemplo 2-14		$Pd(PPh_3)_4$, ácido 3-metoxi-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.19 minutos. (G)	428.2
Ejemplo 2-15		$Pd(PPh_3)_4$, ácido 3-ciano-bencen-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	0.98 minutos. (B)	423.2

Ejemplo	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
Ejemplo 2-16		$Pd(PPh_3)_4$, ácido 3-cloro-5-fluoro-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.45 minutos. (B)	450.1
Ejemplo 2-17		$Pd(PPh_3)_4$, ácido 2-(trifluoro-metil)-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.37 minutos. (B)	466.1

Ejemplo	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
Ejemplo 2-18		$Pd(PPh_3)_4$, ácido 2-ciano-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.01 minutos. (B)	423.2
Ejemplo 2-19		$Pd(PPh_3)_4$, ácido 2-etoxi-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo.	1.29 minutos. (B)	442.2

Ejemplo	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
Ejemplo 2-20		Complejo de $PdCl_2(dppf).CH_2Cl_2$, ácido fenil-d5-borónico, Na_2CO_3 acuoso 2M, 4-(1-(4-bromo-fenil)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoato de (R)-terbutilo	1.42 minutos. (B)	445.2

Ejemplo 2-2: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, J = 7 Hz, 3 H) 2.47 – 2.67 (m, 6 H) 2.84 – 3.02 (m, 2 H) 4.12 – 4.24 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.52 (br d, J = 9.3 Hz, 1 H) 7.24 – 7.26 (m, 2 H) 7.39 – 7.41 (m, 2 H) 7.48 – 7.51 (m, 4 H).

Ejemplo 2-3: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, J = 7 Hz, 3 H) 2.43 – 2.65 (m, 6 H) 2.84 – 3.02 (m, 2 H) 3.67 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.30 (br d, J = 8.6 Hz, 1 H) 7.00 – 7.05 (m, 1 H) 7.26 – 7.29 (m, 3 H) 7.34 – 7.41 (m, 2 H) 7.51 (d, J= 8.3 Hz, 2 H).

Ejemplo 2-4: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, J = 7 Hz, 3 H) 2.44 – 2.65 (m, 6 H) 2.85 – 3.02 (m, 2 H) 3.67 (s, 3

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H) 4.11 – 4.23 (m, 2 H) 4.48 – 4.56 (m, 1 H) 6.30 (br d, J = 9.6 Hz, 1 H) 7.11 – 7.22 (m, 2 H) 7.25 – 7.33 (m, 3 H) 7.40 – 7.45 (m, 1 H) 7.48 – 7.50 (m, 2 H).

Ejemplo 2-5: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, J = 7.2 Hz, 3 H) 2.44 – 2.65 (m, 6 H) 2.86 – 3.02 (m, 2 H) 3.68 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.49 – 4.57 (m, 1 H) 6.31 (br d, J = 8.8 Hz, 1 H) 7.24 – 7.34 (m, 5 H) 7.37 – 7.39 (m, 2 H) 7.45 – 7.47 (m, 1 H).

Ejemplo 2-6: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, J = 7 Hz, 3 H) 2.44 – 2.66 (m, 6 H) 2.84 – 3.01 (m, 2 H) 3.68 (s, 3 H) 3.81 (s, 3 H) 4.11 – 4.23 (m, 2 H) 4.48 – 4.56 (m, 1 H) 6.26 (br d, J = 8.8 Hz, 1 H) 6.97 – 7.04 (m, 2 H) 7.22 (d, J = 8.1 Hz, 2 H) 7.29 – 7.33 (m, 2 H) 7.46 – 7.48 (m, 2 H).

Ejemplo 2-7: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, J = 7.1 Hz, 3 H) 2.26 (s, 3 H) 2.44 – 2.69 (m, 6 H) 2.85 – 3.01 (m, 2 H) 3.68 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.48 – 4.57 (m, 1 H) 6.30 (br d, J = 8.6 Hz, 1 H) 7.21 – 7.26 (m, 8 H).

Ejemplo 2-8: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J* = 7.2 Hz, 3 H) 2.44 – 2.69 (m, 6 H) 2.86 – 3.03 (m, 2 H) 3.68 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.48 – 4.57 (m, 1 H) 6.31 (br d, *J* = 8.8 Hz, 1 H) 6.90 – 7.01 (m, 1 H) 7.05 – 7.08 (m, 1 H) 7.25 – 7.27 (m, 2 H) 7.36 – 7.43 (m, 3 H).

Ejemplo 2-9: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, *J* = 7.2 Hz, 3 H) 2.41 – 2.65 (m, 9 H) 2.84 – 3.00 (m, 2 H) 3.67 (s, 3 H) 4.11 – 4.23 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.29 (br d, *J* = 8.9 Hz, 1 H) 7.16 – 7.39 (m, 6 H) 7.50 – 7.53 (m, 2 H).

Ejemplo 2-10: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J* = 7.2 Hz, 3 H) 2.43 – 2.65 (m, 6 H) 2.84 – 3.02 (m, 2 H) 3.67 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.46 – 4.55 (m, 1 H) 6.33 (br d, *J* = 8.8 Hz, 1 H) 6.76 – 6.80 (m, 1 H) 7.06 – 7.12 (m, 2 H) 7.26 – 7.27 (m, 2 H) 7. 48 (d, *J* = 8.0 Hz, 2 H).

Ejemplo 2-11: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.27 – 1.30 (m, 6 H) 2.44 – 2.57 (m, 4 H) 2.62 – 2.74 (m, 4 H) 2.84 – 3.00 (m, 2 H) 3.67 (s, 3 H) 4.13 – 4.23 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.30 (br d, J = 7.6 Hz, 1 H) 7.17 – 7.26 (m, 3 H) 7.33 – 7.41 (m, 3 H) 7. 52 (d, *J* = 7.8 Hz, 2 H).

Ejemplo 2-12: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.30 (t, *J* = 7.1 Hz, 3 H) 2.41 – 2.65 (m, 6 H) 2.67 – 2.92 (m, 1 H) 3.00 – 3.05 (m, 1 H) 3.68 (s, 3 H) 4.14 – 4.22 (m, 2 H) 4.48 – 4.56 (m, 1 H) 6.33 (br d, *J* = 8.6 Hz, 1 H) 7.32 (d, *J* = 8.3 Hz, 2 H) 7.56 – 7.62 (m, 3 H) 7.89 – 7.91 (m, 1 H) 8.18 – 8.20 (m, 1 H) 8.44 (t, *J* = 8.0 Hz, 1 H).

Ejemplo 2-13: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J* = 7.2 Hz, 3 H) 2.44 – 2.65 (m, 6 H) 2.86 – 2.91 (m, 1 H) 2.98 – 3.03 (m, 1 H) 3.67 (s, 3 H) 4.13 – 4.22 (m, 2 H) 4.47 – 4.56 (m, 1 H) 6.33 (br d, *J* = 8.8 Hz, 1 H) 7.29 (d, *J* = 8.2 Hz, 2 H) 7.53 (d, *J* = 8.2 Hz, 2 H) 7.56 – 7.60 (m, 2 H) 7.75 (d, *J* = 7.6 Hz, 1 H) 7.81 (s, 1 H).

Ejemplo 2-14: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, *J* = 7.2 Hz, 3 H) 2.43 – 2.65 (m, 6 H) 2.84 – 2.89 (m, 1 H) 2.96 – 3.01 (m, 1 H) 3.67 (s, 3 H) 3.86 (s, 3 H) 4.11 – 4.23 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.30 (br d, *J* = 8.8 Hz, 1 H) 6.87 – 6.90 (m, 1 H) 7.10 –

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7.11 (m, 1 H) 7.15 – 7.17 (m, 1 H) 7.24 – 7.26 (m, 2 H) 7.34 (t, *J* = 7.8 Hz, 2 H) 7.51 – 7.53 (m, 2 H).

Ejemplo 2-15: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J* = 7.1 Hz, 3 H) 2.43 – 2.58 (m, 4 H) 2.61 – 2.65 (m, 2 H) 2.84 – 2.91 (m, 1 H) 2.98 – 3.03 (m, 1 H) 3.68 (s, 3 H) 4.12 – 4.24 (m, 2 H) 4.47 – 4.55 (m, 1 H) 6.34 (br d, *J* = 8.8 Hz, 1 H) 7.30 (d, *J* = 8.1 Hz, 2 H) 7.50 (d, *J* = 8.1 Hz, 2 H) 7.51 – 7.63 (m, 2 H) 7.78 – 7.81 (m, 1 H) 7.85 (br s, 1 H).

Ejemplo 2-16: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J* = 7.1 Hz, 3 H) 2.43 – 2.57 (m, 4 H) 2.61 – 2.64 (m, 2 H) 2.87 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.99 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.6 Hz, 1 H) 3.68 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.46 – 4.55 (m, 1 H) 6.34 (br d, *J* = 8.6 Hz, 1 H) 7.05 (dt, *J* = 8.3 y 2.0 Hz, 1 H) 7.15 – 7.19 (m, 1 H) 7.26 – 7.28 (m, 3 H) 7.35 – 7.36 (m, 1 H) 7.45 (d, *J* = 8.1 Hz, 2 H).

Ejemplo 2-17: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J* = 7.1 Hz, 3 H) 2.43 –2.69 (m, 6 H) 2.90 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.99 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.8 Hz, 1 H) 3.68 (s, 3 H) 4.12 – 4.23 (m, 2 H) 4.49 – 4.57 (m, 1 H) 6.31 (br d, *J* = 8.6 Hz, 1 H) 7.20 – 7.26 (m, 4 H) 7.32 (d, *J* = 7.6 Hz, 1 H) 7.44 – 7.47 (m, 1 H) 7.53 – 7.57 (m, 1 H) 7.73 (d, *J* = 7.6 Hz, 2 H).

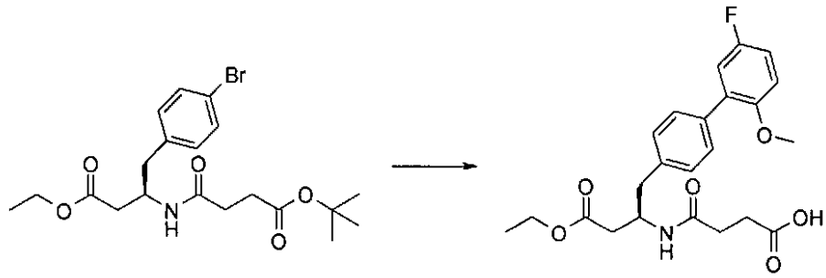
Ejemplo 2-18: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J* = 7.2 Hz, 3 H) 2.44 –2.65 (m, 6 H) 2.91 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 3.01 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.6 Hz, 1 H) 3.68 (s, 3 H) 4.12 – 4.24 (m, 2 H) 4.48 – 4.57 (m, 1 H) 6.34 (br d,

J = 8.6 Hz, 1 H) 7.32 (d, J = 8.1 Hz, 2 H) 7.41 – 7.56 (m, 2 H) 7.62 – 7.66 (m, 1 H) 7.75 – 7.77 (m, 1 H) 7.81 – 7.84 (m, 2 H).

Ejemplo 2-19: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, J = 7.2 Hz, 3 H) 1.35 (t, J = 6.9 Hz, 3 H) 2.44 – 2.53 (m, 4 H) 2.44 – 2.53 (m, 4 H) 2.86 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.1 Hz, 1 H) 2.98 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.1 Hz, 1 H) 3.67 (s, 3 H) 3.99 – 4.23 (m, 4 H) 4.48 – 4.56 (m, 1 H) 6.27 (br d, J = 8.6 Hz, 1 H) 6.94 – 7.04 (m, 2 H) 7.20 – 7.22 (m, 2 H) 7.27 – 7.33 (m, 2 H) 7.41 – 7.52 (m, 2 H).

Ejemplo 2-20: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, J = 7.2 Hz, 3 H) 1.43 (s, 9 H) 2.36 –2.56 (m, 6 H) 2.84 – 3.01 (m, 4 H) 4.11 – 4.22 (m, 2 H) 4.47 – 4.56 (m, 1 H) 6.30 – 6.35 (m, 1 H) 7.25 – 7.27 (m, 2 H) 7.51 – 7 .54 (m, 2 H).

Ejemplo 2-21: Síntesis de ácido (R)-4-(4-etoxi-1-(5'-fluoro-2'-metoxi-bifenil-4-il)-4-oxo-butan-2-il-amino)-4-oxo-butanoico



A una solución del 4-(1-(4-bromo-fenil)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoato de (R)-terbutilo, el intermediario 9, (100 miligramos, 0.23 milimoles), y ácido 5-fluoro-2-metoxi-fenil-borónico (57.6 miligramos, 0.34 milimoles) en tolueno (1 mililitro), y EtOH (0.1 mililitros), se le agregan $Pd(PPh_3)_4$ (26.1 miligramos, 0.023

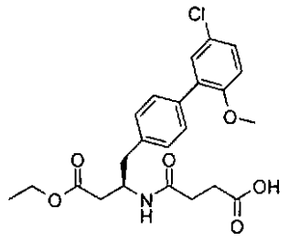
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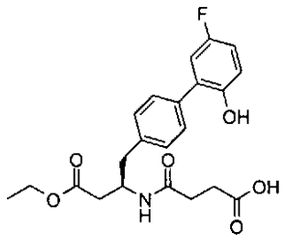
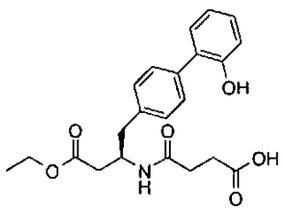
milimoles), y Na_2CO_3 (47.9 miligramos, 0.45 milimoles). Después de agitar a 95°C bajo nitrógeno durante 18 horas, la solución se enfría a temperatura ambiente, y entonces se apaga con HCl acuoso 1M. El producto crudo se diluye con acetato de etilo, la capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea sobre gel de sílice (eluyente: heptano/EtOAc = 100:0 a 30:70), para dar 4-(4-etoxi-1-(5'-fluoro-2'-metoxi-bifenil-4-il)-4-oxo-butan-2-il-amino)-4-oxo-butanoato de (R)-terbutilo (65 miligramos). HPLC - tiempo de retención = 1.44 minutos (condición B); MS (m+1) = 488.3; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.32 (t, *J*=7.1 Hz, 3 H) 1.48 (s, 9 H) 2.41 - 2.48 (m, 2 H) 2.51 - 2.63 (m, 4 H) 2.90 (dd, *J*=13.6, 6 Hz, 1 H) 3.02 (dd, *J*=13.6, 6 Hz, 1 H) 3.81 (s, 3 H) 4.14 - 4.29 (m, 2 H) 4.49 - 4.63 (m, 1 H) 6.44 (d, *J*=8.6 Hz, 1 H) 6.89 - 6.97 (m, 1 H) 6.98 - 7.05 (m, 1 H) 7.05 - 7.11 (m, 1 H) 7.27 (d, *J*=8.1 Hz, 2 H) 7.49 (d, *J*=8.1 Hz, 2 H).

Una solución del 4-(4-etoxi-1-(5'-fluoro-2'-metoxi-bifenil-4-il)-4-oxo-butan-2-il-amino)-4-oxo-butanoato de (R)-terbutilo, (65 miligramos, 0.13 milimoles) en HCl 4M en 1,4-dioxano (671 microlitros, 2.68 milimoles), se agita a temperatura ambiente. Después de agitar durante 1 hora, la mezcla de reacción se concentra bajo presión reducida. El residuo obtenido se purifica mediante HPLC de fase inversa (SunFire C18, H_2O (ácido trifluoro-acético al 0.1 por ciento)/CH_3CN), y se liofiliza, para dar el ácido (R)-4-(4-etoxi-1-(5'-

fluoro-2'-metoxi-bifenil-4-il)-4-oxo-butan-2-il-amino)-4-oxo-butanoico (23 miligramos). HPLC - tiempo de retención = 1.66 minutos (condición D); MS (m+1) = 432.3; ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.17 (t, *J*=7.1 Hz, 3 H) 2.21 - 2.32 (m, 2 H) 2.32 - 2.40 (m, 2 H) 2.40 - 2.48 (m, 2 H) 2.77 (d, *J*=6.8 Hz, 2 H) 3.74 (s, 3 H) 4.03 (q, *J*=7.1 Hz, 2 H) 4.19 - 4.33 (m, 1 H) 7.04 - 7.20 (m, 3 H) 7.23 (d, *J*=8.1 Hz, 2 H) 7.43 (d, *J*=8.1 Hz, 2 H) 7.93 (d, *J*=8.3 Hz, 1 H)

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 2-21:

Ejemplo	Producto	Reactivo	LCMS-RT (condición)	MS (M+1)
Ejemplo 2-22	 ácido (R)-4-(1-(5'-cloro-2'-metoxi-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico	$Pd(PPh_3)_4$, ácido 5-cloro-2-metoxi-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(1-(4-bromo-fenil)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoato de (R)-terbutilo.	1.63 minutos. (D)	448.2

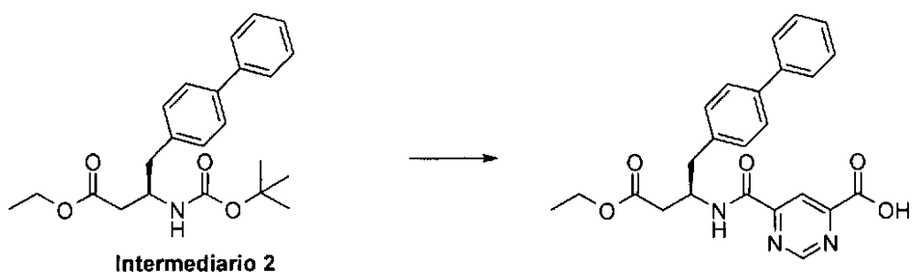
Ejemplo	Producto	Reactivo	LCMS-RT (condición)	MS (M+1)
Ejemplo 2-23	 ácido (R)-4-(4-etoxi-1-(5'-fluoro-2'-hidroxi-bifenil-4-il)-4-oxo-butan-2-il-amino)-4-oxo-butanoico	$Pd(PPh_3)_4$, ácido 5-fluoro-2-hidroxi-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(1-(4-bromo-fenil)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoato de (R)-terbutilo.	1.29 minutos. (A)	418.3
Ejemplo 2-24	 ácido (R)-4-(4-etoxi-1-(2'-hidroxi-bifenil-4-il)-4-oxo-butan-2-il-amino)-4-oxo-butanoico	$Pd(PPh_3)_4$, ácido 2-hidroxi-fenil-borónico, Na_2CO_3 acuoso 2M, 4-(1-(4-bromo-fenil)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoato de (R)-terbutilo.	1.65 minutos. (D)	400.3

Ejemplo 2-22: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.23 (t, *J*=7.1 Hz, 3 H) 2.36 - 2.58 (m, 6 H) 2.85 (d, *J*=7.1 Hz, 2 H) 3.76 (s, 3 H) 4.10 (q, *J*=7.1 Hz, 2 H) 4.40 - 4.57 (m, 1 H) 7.01 (d, *J*=8.6 Hz, 1 H) 7.17 - 7.30 (m, 4 H) 7.39 (d, *J*=8.1 Hz, 2 H)

Ejemplo 2-23: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.16 (t, *J*=7.2 Hz, 1 H) 2.23 - 2.30 (m, 2 H) 2.34 - 2.40 (m, 2 H) 2.40 - 2.45 (m, 2 H) 2.75 (dd, *J*=6.6, 3.3 Hz, 2 H) 4.02 (q, *J*=7.2 Hz, 2 H) 4.19 - 4.30 (m, 1 H) 6.87 - 6.94 (m, 1 H) 6.93 - 7.02 (m, 1 H) 7.07 (dd, *J*=9.7, 3.2 Hz, 1 H) 7.22 (d, *J*=8.1 Hz, 2 H) 7.49 (d, *J*=8.1 Hz, 2 H) 7.94 (d, *J*=8.1 Hz, 1 H) 9.52 (s, 1 H)

Ejemplo 2-24: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.16 (t, *J*=7.1 Hz, 3 H) 2.22 - 2.32 (m, 2 H) 2.34 - 2.41 (m, 2 H) 2.43 (dd, *J*=6.8, 3.3 Hz, 2 H) 2.68 - 2.82 (m, 2 H) 4.02 (q, *J*=7.1 Hz, 2 H) 4.17 - 4.35 (m, 1 H) 6.80 - 6.89 (m, 1 H) 6.93 (d, *J*=7.1 Hz, 1 H) 7.09 - 7.17 (m, 1 H) 7.17 - 7.29 (m, 3 H) 7.46 (d, *J*=8.3 Hz, 2 H) 7.93 (d, *J*=8.1 Hz, 1 H) 9.46 (br. s., 1 H)

Ejemplo 3-1: Síntesis de ácido (R)-6-(1-(bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-carbamoil)-pirimidin-4-carboxílico



Intermediario 2

Al 4-(bifenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-etilo (300 miligramos, 0.782 milimoles), se le agrega una solución de

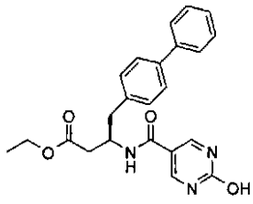
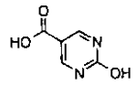
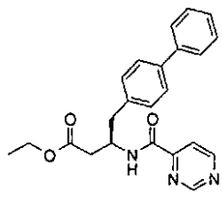
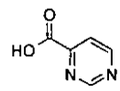
HCl 4M en 1,4-dioxano (3.92 mililitros, 15.65 milimoles) a temperatura ambiente. Después de agitar durante 1 hora, la mezcla de reacción se concentra bajo presión reducida, para dar el clorhidrato de etil-éster del ácido (R)-3-amino-4-bifenil-4-il-butírico.

En seguida, a una suspensión del ácido pirimidin-4,6-dicarboxílico (325 miligramos, 1.935 milimoles), clorhidrato de etil-éster del ácido (R)-3-amino-4-bifenil-4-il-butírico (250 miligramos, 0.774 milimoles), clorhidrato de WSC (148 miligramos, 0.774 milimoles), y HOAt (105 miligramos, 0.774 milimoles) en N,N-dimetil-formamida (4 mililitros), y H_2O (1 mililitro), se le agrega di-isopropil-etil-amina (0.135 mililitros, 0.774 milimoles). Después de agitar durante 14 horas, la reacción se apaga con H_2O, y los productos se extraen con EtOAc, se lavan con salmuera, se secan sobre Na_2SO_4, se filtran, y se concentran bajo presión reducida.

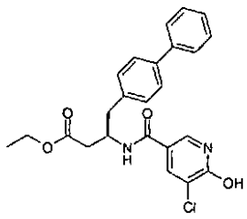
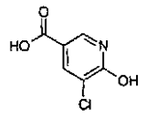
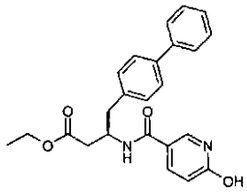
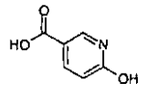
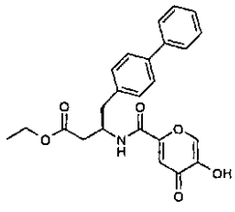
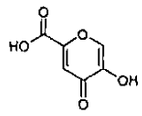
El residuo obtenido se purifica mediante HPLC de fase inversa (SunFire C18, H_2O (ácido trifluoro-acético al 0.1 por ciento)/CH_3CN), y se liofiliza, para dar el ácido (R)-6-(1-(bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-carbamoil)-pirimidin-4-carboxílico (84.8 miligramos). HPLC - tiempo de retención = 1.32 minutos (condición B); MS (m+1) = 434.1; ^{1}H RMN (400 MHz, DMSO-*d6*) δ ppm 1.12 (t, J = 7.0 Hz, 3 H) 2.65 (A de ABX, Jab = 15.4 Hz, Jax = 5.8 Hz, 1 H) 2.73 (B de ABX, Jab = 15.4 Hz, Jbx = 7.9 Hz) 2.91 (A de ABX, Jab = 13.6 Hz, Jax = 6.1 Hz, 1 H) 3.01 (B de ABX, Jab = 13.6 Hz, Jbx = 8.2 Hz, 1 H) 4.01 (q, J = 7.0 Hz, 2 H) 4.59 – 4.68 (m, 1 H) 7.29 – 7.35 (m, 3 H) 7.41 – 7.45 (m, 2 H) 7.55 – 7.63 (m, 4 H) 8.32 (d, J = 1.35 Hz, 1 H) 9.19 (d.

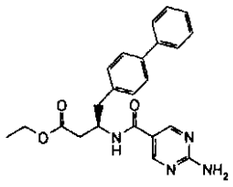
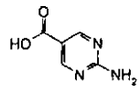
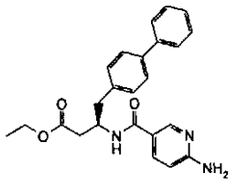
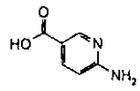
J = 9.1 Hz, 1 H) 9.50 (d, J = 1.35 Hz, 1 H) 14.11 (br s, 1 H).

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 3-1:

Ejemplo #	**Producto**	**Reactivo**	**HPLC-RT (condición)**	**MS (M+1)**
Ejemplo 3-2	 etil-éster del ácido (R)-4-bifenil-4-il-3-[(2-hidroxi-pirimidin-5-carbonil)-amino]-butírico		1.56 minutos. (A)	406.2
Ejemplo 3-3	 etil-éster del ácido (R)-4-bifenil-4-il-3-[(pirimidin-4-carbonil)-amino]-butírico		1.73 minutos. (A)	390

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Ejemplo #	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
Ejemplo 3-4	 4-(bifenil-4-il)-3-(5-cloro-6-hidroxi-nicotinamido)-butanoato de (R)-etilo	 PyBOP en lugar de WSC.HCl y HOAt	1.69 minutos. (D)	439.0
Ejemplo 3-5	 4-(bifenil-4-il)-3-(6-hidroxi-nicotinamido)-butanoato de (R)-etilo	 PyBOP en lugar de WSC.HCl, HOAt	1.55 minutos. (B)	405.2
Ejemplo 3-6	 4-(bifenil-4-il)-3-(5-hidroxi-4-oxo-4H-piran-		1.65 minutos. (A)	422.2

Ejemplo #	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
	2-carboxamido)-butanoato de (R)-etilo			
Ejemplo 3-7	 3-(2-amino-pirimidin-5-carboxamido)-4-(bifenil-4-il)-butanoato de (R)-etilo	 PyBOP en lugar de WSC.HCl y HOAt	1.58 minutos. (A)	405.8
Ejemplo 3-8	 3-(6-amino-nicotinamido)-4-(bifenil-4-il)-butanoato de (R)-etilo	 PyBOP en lugar de WSC.HCl y HOAt	1.65 minutos. (A)	404.3

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Ejemplo 3-2: ^{1}H RMN (400 MHz, DMSO-*d6*) δ ppm 1.14 (t, J = 7.1 Hz, 3 H) 2.57 (d, J = 7.1 Hz, 2 H) 2.83 – 2.92 (m, 2 H) 4.03 (q, J = 7.1 Hz, 2 H) 4.43 – 4.52 (m, 1 H) 7.29 – 7.36 (m, 3 H) 7.42 – 7.46 (m, 2 H) 7.58 – 7.65 (m, 4 H) 8.30 (d, J = 8.4 Hz, 1 H) 8.64 (br s, 1 H).

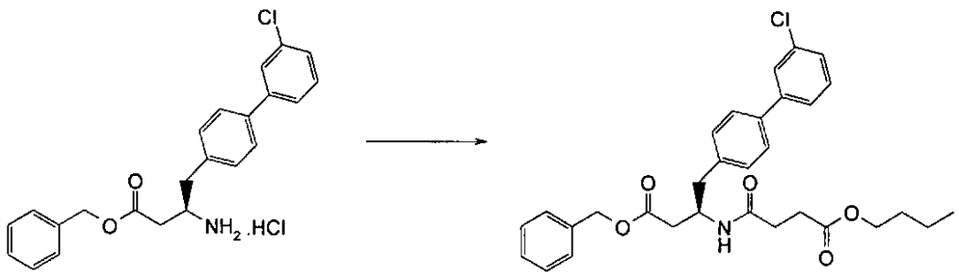
Ejemplo 3-4: ^{1}H RMN (400 MHz, DMSO-*d6*) δ ppm 1.13 (t, J = 7.1 Hz, 3 H) 2.55 (d, J = 6.9 Hz, 2 H) 2.82 – 2.92 (m, 2 H) 4.00 (q, J = 7.1 Hz, 2 H) 4.43 – 4.52 (m, 1 H) 7.29 – 7.35 (m, 3 H) 7.42 – 7.46 (m, 2 H) 7.58 – 7.65 (m, 4 H) 7.93 – 7.96 (m, 1H) 8.10 (d, J = 2.3 Hz, 1 H) 8.25 (d, J = 8.3 Hz, 1 H) 12.53 (d, J = 6.1 Hz, 1 H).

Ejemplo 3-5: ^{1}H RMN (400 MHz, DMSO-*d6*) δ ppm 1.13 (t, J = 7.1 Hz, 3 H) 2.55 (d, J = 7.6 Hz, 2 H) 2.81– 2.92 (m, 2 H) 4.02 (q, J = 7.1 Hz, 2 H) 4.43 – 4.52 (m, 1 H) 7.29 – 7.36 (m, 3 H) 7.42 – 7.46 (m, 2 H) 7.57 – 7.65 (m, 4 H) 7.78 – 7.81 (m, 1H) 7.92 (d, J = 2.3 Hz, 1 H) 8.16 (d, J = 8.1 Hz, 1 H) 11.92 (s, 1 H).

Ejemplo 3-6: ^{1}H RMN (400 MHz, DMSO-*d6*) δ ppm 1.13 (t, J = 7 Hz, 3 H) 2.55 – 2.67 (m, 2 H) 2.83– 2.94 (m, 2 H) 4.02 (q, J = 7 Hz, 2 H) 4.46 – 4.55 (m, 1 H) 6.82 (s, 1 H) 7.28 - 7.35 (m, 3 H) 7.42 – 7.46 (m,2 H) 7.59 (d, J = 8.3 Hz, 2 H) 7.63 (d, J = 7.0 Hz, 2 H) 8.13 (s, 1 H) 8.89 (d, J = 8.6 Hz, 1 H) 9.56 (s, 1 H).

Ejemplo 3-7: ^{1}H RMN (400 MHz, DMSO-*d6*) δ ppm 1.13 (t, J = 7 Hz, 3 H) 2.56 – 2.58 (m, 2 H) 2.83– 2.94 (m, 2 H) 4.02 (q, J = 7 Hz, 2 H) 4.46 – 4.55 (m, 1 H) 7.19 (s, 2 H) 7.30 - 7.35 (m, 3 H) 7.42 – 7.46 (m,2 H) 7.58 – 7.65 (m, 4H) 8.22 (d, J = 8.1 Hz, 1 H) 8.60 (s, 1 H).

Ejemplo 3-9: Síntesis de 3-(4-butoxi-4-oxo-butanamido)-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo

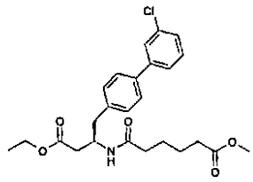
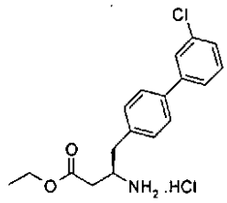
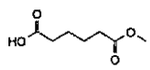
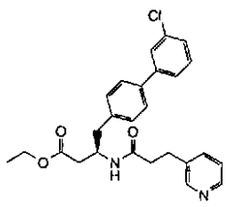
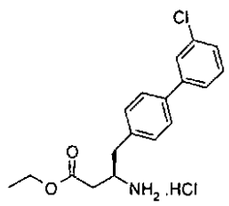
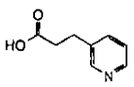


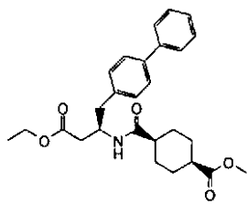
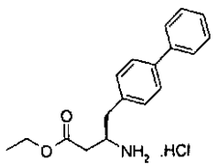
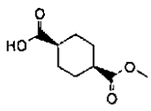
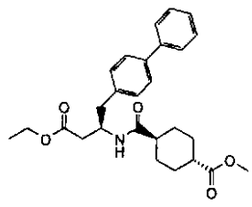
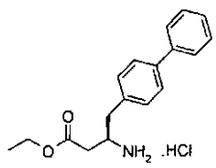
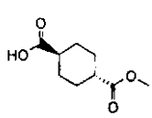
Una mezcla de clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo (150 miligramos, 0.360 milimoles), ácido 4-butoxi-4-oxo-butanoico (107 miligramos, 0.540 milimoles, pureza del 88 por ciento), EDCI (104 miligramos, 0.540 milimoles), di-isopropil-etil-amina (0.094 mililitros, 0.540 milimoles), y HOAt (73.6 miligramos, 0.540 milimoles) en N,N-dimetil-formamida (2 mililitros) se deja agitándose a temperatura ambiente durante 1 hora. La mezcla de reacción se diluye con agua, y entonces el sólido precipitado se recolecta en un embudo, se lava con H_2O, y se seca bajo presión reducida, para dar el producto crudo. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea en gel de sílice (heptano/EtOAc = 100:0 a 0:100), para dar el 3-(4-butoxi-4-oxo-butanamido)-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo (178.9 miligramos); HPLC - tiempo de retención = 1.47 minutos (condición B); MS (m+1) = 536.42; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 0.90 – 0.94 (m, 3 H) 1.31 – 1.40 (m, 2 H) 1.56 – 1.63 (m, 2 H) 2.39 – 2.42 (m, 2 H) 2.48 – 2.62 (m, 4 H) 2.84 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.1 Hz, 1 H) 2.97 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.6 Hz, 1 H) 4.07 (t, J = 6.7 Hz, 2 H) 4.48 – 4.56 (m, 1 H) 5.12 (A de AB, J = 12.1 Hz, 1 H) 5.18 (B de AB, J = 12.1 Hz,

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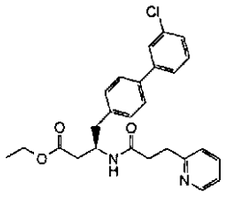
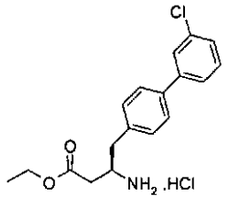
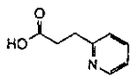
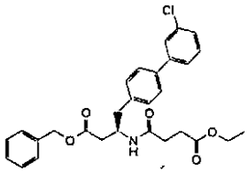
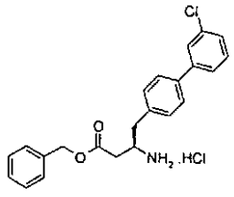
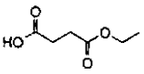
1 H) 6.27 (br d, *J* = 7.7 Hz, 1 H) 7.20 (d, *J* = 8.3 Hz, 1 H) 7.29 – 7.39 (m, 7 H) 7.42 – 7.47 (m, 3 H) 7.54 – 7.55 (m, 1 H).

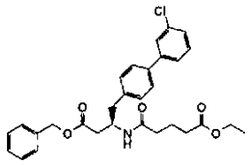
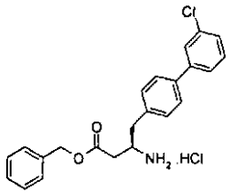
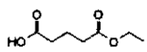
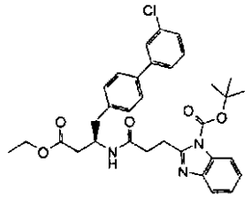
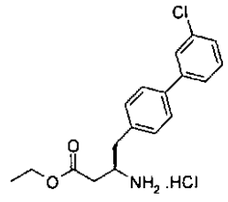
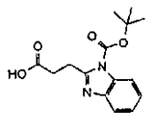
Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 3-8:

Ejemplo #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
Ejemplo 3-10	 6-(1-(3'-cloro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-6-oxo-hexanoato de (R)-metilo		 EDCI, HOAt, DIPEA, N,N-dimetil-formamida, RT	1.40 minutos (B)	460.5
Ejemplo 3-11	 4-(3'-cloro-bifenil-4-il)-3-(3-(piridin-3-il)-		 EDCI, HOAt, N,N-dimetil-formamida,	1.56 minutos (A)	451.3

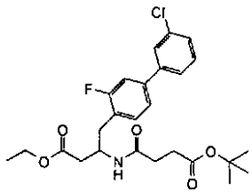
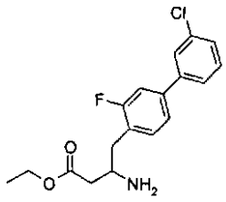
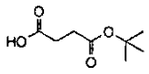
Ejemplo #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
	propanamido)-butanoato de (R)-etilo		RT		
Ejemplo 3-12	 4-((R)-1-(bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-carbamoil)-ciclohexan-carboxilato de (1S,4s)-metilo		 EDCI, HOAt, DIPEA, N,N-dimetil-formamida, RT	1.42 minutos (B)	452.2
Ejemplo 3-13	 4-((R)-1-(bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-		 EDCI, HOAt, DIPEA, N,N-dimetil-	1.42 minutos (B)	452.3

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Ejemplo #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
	carbamoil)-ciclohexan-carboxilato de (1R,4R)-metilo		formamida, RT		
Ejemplo 3-14	 4-(3'-cloro-bifenil-4-il)-3-(3-(piridin-2-il)-propanamido)-butanoato de (R)-etilo		 EDCI, HOAt, DIPEA, N,N-dimetil-formamida, RT	1.61 minutos (A)	451.3
Ejemplo 3-16	 4-(3'-cloro-bifenil-4-il)-3-(4-etoxi-4-oxo-butanamido)-		 EDCI, HOAt, DIPEA, N,N-dimetil-formamida,	1.56 minutos (B)	508.3

Ejemplo #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
	butanoato de (R)-bencilo		RT		
Ejemplo 3-17	 5-(4-(benciloxi)-1-(3'-cloro-bifenil-4-il)-4-oxo-butan-2-il-amino)-5-oxo-pentanoato de (R)-etilo		 EDCI, HOAt, DIPEA, N,N-dimetil-formamida, RT	1.57 minutos (B)	522.4
Ejemplo 3-18	 2-(3-(1-(3'-cloro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-3-		 EDCI, HOAt, DIPEA, tetrahidro-furano, RT	0.80 minutos (B)	590.3

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Ejemplo #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
	oxopropil)-1H-benzo-[d]-imidazol-1-carboxilato de (R)-terbutilo				
Ejemplo 3-19	 4-(1-(3'-cloro-3-fluoro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoato de terbutilo		 EDCI, HOAt, N,N-dimetil-formamida, RT	1.46 minutos (B)	492.5

Ejemplo 3-10: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.29 (t, J = 7.2 Hz, 3 H) 1.58 – 1.64 (m, 4 H) 2.14 – 2.18 (m, 2 H) 2.28 – 2.32 (m, 2 H) 2.49 (A de ABX, J_{ab} = 16.2 Hz, J_{ax} = 5.3 Hz, 1 H) 2.53 (B de ABX, J_{ab} = 16.2 Hz, J_{bx} = 5.3 Hz, 1 H) 2.87 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.1 Hz, 1 H) 2.99 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.8

Hz, 1 H) 3.65 (s, 3 H) 4.11 - 4.23 (m, 2 H) 4.48 - 4.56 (m, 1 H) 6.18 (br d, J = 8.8 Hz, 1 H) 7.26 - 7.37 (m, 4 H) 7.43 – 7.52 (m, 3 H) 7.56 (br t, J = 1.8 Hz, 1 H)

Ejemplo 3-11: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.27 (t, J = 7.1 Hz, 3 H) 2.40 – 2.51 (m, 4 H) 2.77 – 2.83 (m, 1 H) 2.91 – 2.97 (m, 3 H) 4.08 - 4.20 (m, 2 H) 4.46 - 4.54 (m, 1 H) 6.22 – 6.24 (m, 1 H) 7.18 - 7.23 (m, 3 H) 7.29 - 7.37 (m, 2 H) 7.43 - 7.49 (m, 3 H) 7.55 – 7.57 (m, 2 H) 8.44 (d, J = 4.8 Hz, 1 H) 8.48 (s, 1 H).

Ejemplo 3-12: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.29 (t, J = 7.1 Hz, 3 H) 1.53 – 2.20 (m, 9 H) 2.46 – 2.57 (m, 3 H) 2.86 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.98 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.6 Hz, 1 H) 3.65 (s, 3 H) 4.11 - 4.23 (m, 2 H) 4.47 - 4.55 (m, 1 H) 6.23 (br d, J = 8.6 Hz, 1 H) 7.24 – 7.26 (m, 2 H) 7.31 - 7.35 (m, 1 H) 7.41 – 7.45 (m, 2 H) 7.51 – 7.59 (m, 4 H).

Ejemplo 3-13: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.29 (t, J = 7.2 Hz, 3 H) 1.36 – 1.51 (m, 4 H) 1.84 – 1.94 (m, 2 H) 1.98 – 2.06 (m, 3 H) 2.24 – 2.32 (m, 1H) 2.50 (A de ABX, J_{ab} = 16.2 Hz, J_{ax} = 5.3 Hz, 1 H) 2.53 (B de ABX, J_{ab} = 16.2 Hz, J_{bx} = 5.1 Hz, 1 H) 2.86 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.98 (B de ABX, J_{ab} = 13.6 Hz, Jbx = 6.6 Hz, 1 H) 3.66 (s, 3 H) 4.11 - 4.23 (m, 2 H) 4.46 - 4.55 (m, 1 H) 6.19 (br d, J = 8.8 Hz, 1 H) 7.24 – 7.26 (m, 2 H) 7.31 - 7.36 (m, 1 H) 7.41 – 7.45 (m, 2 H) 7.51 – 7.58 (m, 4 H).

Ejemplo 3-14: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.26 (t, J = 7.2 Hz, 3 H) 2.41 – 2.51 (m, 4 H) 2.62 – 2.66 (m, 2 H) 2.84 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.6 Hz, 1 H) 2.92 (B de ABX, J_{ab} = 13.6

Hz, J_{bx} = 6.6 Hz, 1 H) 3.06 – 3.10 (m, 2 H) 4.08 - 4.19 (m, 2 H) 4.46 - 4.55 (m, 1 H) 6.78 (d, *J* = 8.9 Hz, 1 H) 7.10 – 7.12 (m, 1 H) 7.16 (d, *J* = 7.8 Hz, 1 H) 7.20 - 7.22 (m, 2 H) 7.29 - 7.31 (m, 1 H) 7.35 (t, *J* = 7.7 Hz, 1 H) 7.42 - 7.47 (m, 3 H) 7.54 – 7.59 (m, 2 H) 8.48 (d, *J* = 1.0 Hz, 1 H).

Ejemplo 3-16: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.24 (t, *J* = 7.1 Hz, 3 H) 2.38 – 2.42 (m, 2 H) 2.49 – 2.61 (m, 4 H) 2.82 – 3.00 (m, 2 H) 4.12 (q, *J* = 7.1 Hz, 2 H) 4.47 – 4.56 (m, 1 H) 5.12 (A de AB, *J* = 12.3 Hz, 1 H) 5.18 (B de AB, *J* = 12.3 Hz, 1 H) 6.26 (br d, *J* = 8.6 Hz, 1 H) 7.20 (d, *J* = 8.3 Hz, 2 H) 7.29 - 7.46 (m, 10 H) 7.54 – 7.54 (m, 1 H).

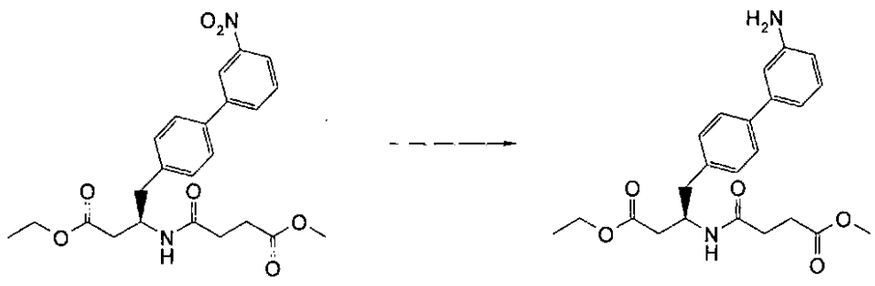
Ejemplo 3-17: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.23 (t, *J* = 7.2 Hz, 3 H) 1.86 – 1.92 (m, 2 H) 2.14 – 2.18 (m, 2 H) 2.24 – 2.28 (m, 2 H) 2.50 – 2.63 (m, 2 H) 2.82 – 2.99 (m, 2 H) 4.11 (q, *J* = 7.2 Hz, 2 H) 4.53 – 4.54 (m, 1 H) 5.12 (A de AB, *J* = 12.1 Hz, 1 H) 5.18 (B de AB, *J* = 12.1 Hz, 1 H) 6.12 – 6.14 (m, 1 H) 7.19 – 7.54 (m, 13 H).

Ejemplo 3-18: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.26 (t, *J* = 7.2 Hz, 3 H) 1.67 (s, 9 H) 2.46 – 2.57 (m, 2 H) 2.74 – 2.96 (m, 4 H) 3.41 – 3.45 (m, 2 H) 4.09 – 4.17 (m, 2 H) 4.50 – 4.59 (m, 1 H) 6.95 (br d, *J* = 8.6 Hz, 1 H) 7.18 (d, *J* = 8.1 Hz, 2 H) 7.27 – 7.42 (m, 7 H) 7.51 (t, *J* = 1.8 Hz, 1 H) 7.61 – 7.65 (m, 1 H) 7.86 – 7.93 (m, 1 H).

Ejemplo 3-19: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.28 (t, *J* = 7.2 Hz, 3 H) 1.43 (s, 9 H) 2.37 – 2.40 (m, 2 H) 2.50 – 2.59 (m,

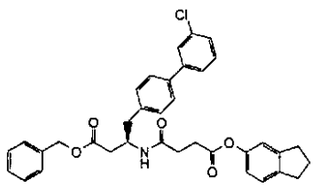
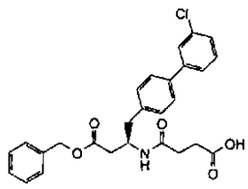
4 H) 2.98 (d, *J* = 7.3 Hz, 2 H) 4.13 – 4.21 (m, 2 H) 4.48 – 4.56 (m, 1 H) 6.35 (br d, *J* = 8.8 Hz, 1 H) 7.22 – 7.44 (m, 6 H) 7.54 – 7.54 (m, 1 H).

Ejemplo 3-20: Síntesis de 4-(3'-amino-bifenil-4-il)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo



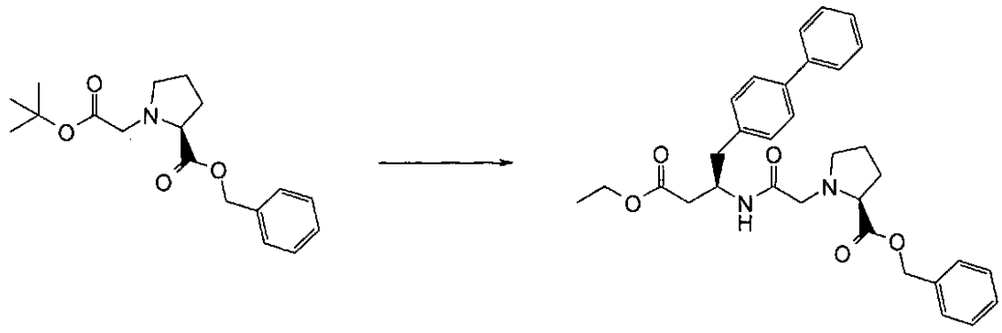
Una suspensión de 3-(4-metoxi-4-oxo-butanamido)-4-(3'-nitro-bifenil-4-il)-butanoato de (R)-etilo (123 miligramos, 0.278 milimoles), y Pd/C (59.2 miligramos, 0.028 milimoles) en EtOH (2 mililitros) se deja agitándose bajo hidrógeno a temperatura ambiente durante 5.5 horas. La mezcla de reacción se filtra, y la solución se concentra, para dar el 4-(3'-amino-bifenil-4-il)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo (105 miligramos); HPLC - tiempo de retención = 0.84 minutos (condición B); MS (m+1) = 413.1; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, *J* = 7.2 Hz, 3 H) 2.41 – 2.65 (m, 6 H) 2.85 – 3.00 (m, 2 H) 3.67 (s, 3 H) 4.11 – 4.22 (m, 2 H) 4.46 – 4.54 (m, 1 H) 6.31 (br d, *J* = 8.8 Hz, 1 H) 6.71 – 6.74 (m, 1 H) 6.95 – 7.02 (m,2 H) 7.21 – 7.25 (m, 3 H) 7.48 – 7.50 (m, 2 H).

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 3-20:

Ejemplo #	Producto	Condición	HPLC-RT (condición)	MS (M+1)
Ejemplo 3-22	 4-(3'-cloro-bifenil-4-il)-3-(4-(2,3-dihidro-1H-inden-5-iloxi)-4-oxo-butanamido)-butanoato de (R)-bencilo	 Ejemplo BB-13, PyBOP, indanol, DCM, RT	1.73 minutos. (B)	596.5

Ejemplo 3-22: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 2.03 – 2.11 (m, 2H) 2.48 – 2.62 (m, 4 H) 2.81 – 2.90 (m, 7 H) 2.95 – 3.00 (m, 1 H) 4.49 – 4.58 (m, 1 H) 5.07 – 5.18 (m, 2 H) 6.23 (br d, *J* = 8.6 Hz, 1 H) 6.79 – 6.82 (m, 1 H) 6.92 (s, 1 H) 7.15 – 7.20 (m, 3 H) 7.29 – 7.45 (m, 10 H) 7.52 – 7.53 (m, 1 H)

Ejemplo 3-23: Síntesis de sal de ácido trifluoro-acético del 1-(2-((R)-1-(bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-2-oxo-etil)-pirrolidin-2-carboxilato de (S)-bencilo

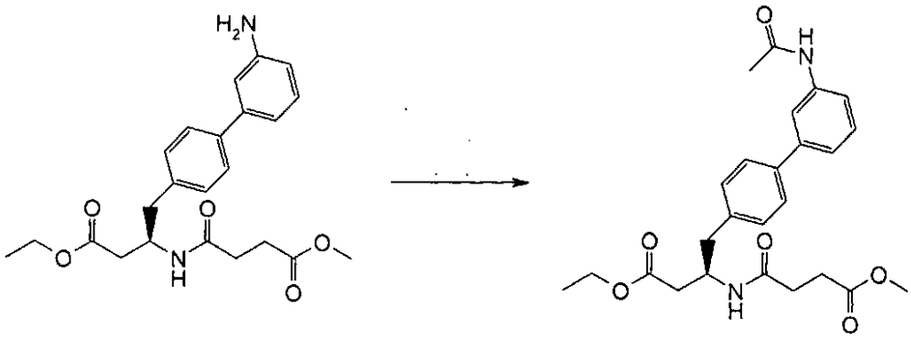


A una solución de 1-(2-terbutoxi-2-oxo-etil)-pirrolidin-2-carboxilato de (S)-bencilo (200 miligramos, 0.626 milimoles), y trietil-silano (0.250 mililitros, 1.565 milimoles) en dicloro-metano (3 mililitros), se le agrega ácido trifluoro-acético (0.965 mililitros, 12.52 milimoles) a temperatura ambiente. Después de agitar durante 24 horas, la reacción se concentra, para dar el producto crudo.

A una suspensión del producto crudo, se le agregan clorhidrato de 3-amino-4-(bifenil-4-il)-butanoato de (R)-etilo (266 miligramos, 0.832 milimoles), WSC.HCl (0.180 gramos, 0.939 milimoles), y HOAt (128 miligramos, 0.939 milimoles) en N,N-dimetil-formamida (4 mililitros) y di-isopropil-etil-amina (0.328 mililitros, 1.878 milimoles). Después de agitar durante 4 horas, la reacción se diluye con H_2O y EtOAc. Los productos se extraen con EtOAc, se lavan con salmuera, se secan sobre Na_2SO_4, se filtran, y se concentran. El producto crudo se somete dos veces a cromatografía en columna (heptano/EtOAc = 100:0 a 0:100). Entonces, el producto obtenido se purifica mediante HPLC de preparación utilizando un gradiente del 20 por ciento de MeCN/agua (ácido trifluoro-acético al 0.1 por ciento) al 100 por ciento de MeCN, para dar la sal de ácido trifluoro-acético del

1-(2-((R)-1-(bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-2-oxo-etil)-pirrolidin-2-carboxilato de (S)-bencilo (28.5 miligramos) como un sólido amarillo pálido; HPLC - tiempo de retención = 1.84 minutos (condición D); MS (m+1) = 529.3; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.25 – 1.28 (m, 3 H) 1.74 – 1.85 (m, 2 H) 1.91 – 1.98 (m, 1 H) 2.09 – 2.19 (m, 1 H) 2.35 – 2.41 (m, 1 H) 2.46 (A de ABX, Jab = 15.7 Hz, Jax = 6.6 Hz, 1 H) 2.59 (B de ABX, J_{ab} = 13.7 Hz, J_{bx} = 5.7 Hz, 1 H) 2.78 – 2.83 (m, 1 H) 2.86 (A de ABX, J_{ab} = 13.8 Hz, J_{ax} = 8.1 Hz, 1 H) 2.99 (B de ABX, J_{ab} = 13.7 Hz, J_{bx} = 6.4 Hz, 1 H) 3.08 (A de AB, *J* = 16.5 Hz, 1 H) 3.35 (B de AB, *J* = 16.5 Hz, 1 H) 3.41 (dd, *J* = 9.1 y 5.1 Hz, 1 H) 4.11 – 4.20 (m, 2 H) 4.46 – 4.55 (m, 1 H) 5.10 (A de AB, *J* = 12.4 Hz, 1 H) 5.13 (B de AB, *J* = 12.4 Hz, 1 H) 7.26 – 7.27 (m, 2 H) 7.31 – 7.38 (m, 6 H) 7.40 – 7.44 (m, 2 H) 7.49 – 7.56 (m, 4 H) 7.74 (br d, *J* = 8.6 Hz, 1 H).

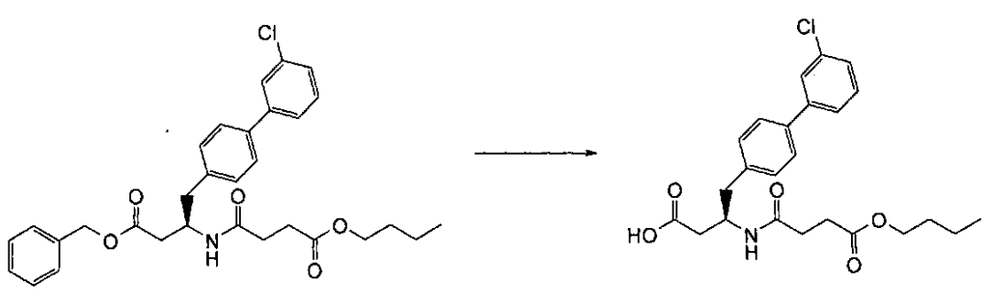
Ejemplo 3-24: Síntesis de 4-(3'-acetamido-bifenil-4-il)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo



Una solución del 4-(3'-amino-bifenil-4-il)-3-(4-metoxi-4-oxo-

butanamido)-butanoato de (R)-etilo (70.5 miligramos, 0.171 milimoles), Et_3N (0.027 mililitros, 0.205 milimoles), y Ac_2O (0.019 mililitros, 0.205 milimoles) en dicloro-metano (1.7 mililitros) se deja agitándose a temperatura ambiente durante 65 horas. La mezcla de reacción se diluye con agua. Los productos se extraen con dicloro-metano en un separador de fases, y se concentran para dar el producto crudo (98 miligramos). El producto crudo se purifica mediante cromatografía en columna por evaporación instantánea en gel de sílice (eluyente: DCM/MeOH = 10:1), para dar el 4-(3'-acetamido-bifenil-4-il)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo (71.5 miligramos); HPLC - tiempo de retención = 1.45 minutos (condición D); MS (m+1) = 455.4; ^{1}H RMN (400 MHz, CD3CN, mezcla de rotámeros, datos para el rotámero mayor) δ ppm 1.21 (t, *J* = 7.1 Hz, 3 H) 2.07 (s, 3 H) 2.31 – 2.34 (m, 2 H) 2.40 – 2.51 (m, 4 H) 2.82 – 2.84 (m, 2 H) 3.58 (s, 3 H) 4.07 (q, *J* = 7.1 Hz, 2 H) 4.34 – 4.43 (m, 1 H) 6.46 (br d, *J* = 8.9 Hz, 1 H) 7.28 – 7.39 (m, 4 H) 7.52 – 7.54 (m, 3 H) 7.80 (s, 1 H) 8.37 (br s, 1 H).

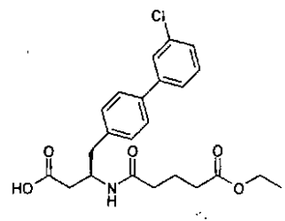
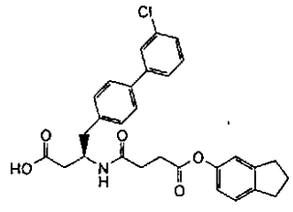
Ejemplo 3-25: Síntesis de ácido (R)-3-(4-butoxi-4-oxo-butanamido)-4-(3'-cloro-bifenil-4-il)-butanoico



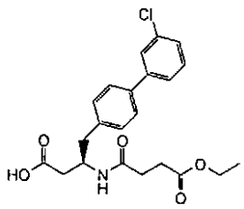
Una suspensión del 3-(4-butoxi-4-oxo-butanamido)-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo (178.9 miligramos, 0.334 milimoles), y Pd/C (71.0 miligramos, 0.033 milimoles) en EtOAc (3 mililitros) se deja agitándose bajo hidrógeno a temperatura ambiente durante 1.5 horas. La mezcla de reacción se filtra, y se concentra, para dar el producto crudo. El residuo resultante se purifica mediante HPLC de preparación utilizando un gradiente del 20 por ciento de MeCN/agua (ácido trifluoro-acético al 0.1 por ciento) al 100 por ciento de MeCN, para dar el ácido (R)-3-(4-butoxi-4-oxo-butanamido)-4-(3'-cloro-bifenil-4-il)-butanoico (90.7 miligramos) como un sólido blanco; HPLC - tiempo de retención = 1.27 minutos (condición B); MS (m+1) = 446.24; ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 0.91 (t, J = 7.5 Hz, 3 H) 1.31 - 1.40 (m, 2 H) 1.55 - 1.62 (m, 2 H) 2.43 - 2.47 (m, 2 H) 2.52 - 2.69 (m, 4 H) 2.93 (A de ABX, J_{ab} = 13.7 Hz, J_{ax} = 7.7 Hz, 1 H) 3.00 (B de ABX, J_{ab} = 13.7 Hz, J_{bx} = 6.8 Hz, 1 H) 4.07 (t, J = 6.7 Hz, 2 H) 4.49 – 4.57 (m, 1 H) 6.31 (br d, J = 8.6 Hz, 1 H) 7.26 - 7.37 (m, 4 H) 7.43 - 7.46 (m, 1 H) 7.49 - 7.52 (m, 2 H) 7.55 (br t, J = 1.8 Hz, 1 H).

HPLC quiral - tiempo de retención = 4.33 minutos. Columna: Daicel CHIRALPAK IA (4.6 x 100 milímetros); velocidad de flujo = 1 mililitro/minuto; eluyente: EtOH (que contiene ácido trifluoro-acético al 0.1 por ciento)/heptano = 10/90 a 70/30 en 10 minutos (gradiente lineal).

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 3-24:

Ejemplo #	Producto	Condición	HPLC-RT (condición)	MS (M+1)
Ejemplo 3-26	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-(5-etoxi-5-oxo-pentanamido)-butanoico	Pd/C, H_2, EtOAc, RT	1.08 minutos. (B)	432.4
Ejemplo 3-27	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-(4-(2,3-dihidro-1H-inden-5-iloxi)-4-oxo-butanamido)-butanoico	Pd/C, H_2, EtOAc, acetona, RT	1.36 minutos. (B)	506.4

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Ejemplo #	Producto	Condición	HPLC-RT (condición)	MS (M+1)
Ejemplo 3-28	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-(4-etoxi-4-oxo-butanamido)-butanoico	Pd/C, H_2, EtOAc, RT	1.00 minutos. (B)	418.4

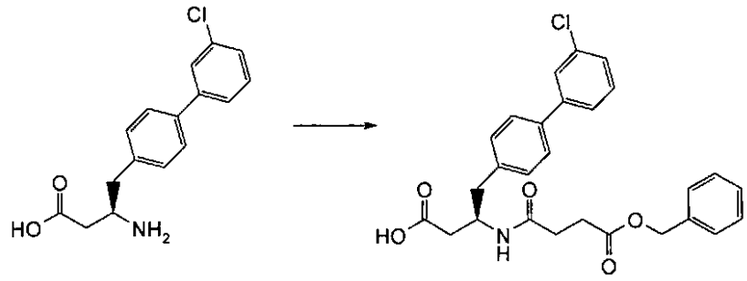
Ejemplo 3-26: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.23 (t, J = 7.1 Hz, 3 H) 1.86 - 1.93 (m, 2 H) 2.57 (A de ABX, J_{ab} = 16.3 Hz, J_{ax} = 5.7 Hz, 1 H) 2.64 (B de ABX, J_{ab} = 16.3 Hz, J_{bx} = 5.2 Hz, 1 H) 2.94 (A de ABX, J_{ab} = 13.7 Hz, J_{ax} = 7.6 Hz, 1 H) 2.99 (B de ABX, J_{ab} = 13.7 Hz, J_{bx} = 7.2 Hz, 1 H) 4.10 (q, J = 7.1 Hz, 2 H) 4.51 – 4.60 (m, 1 H) 6.17 (br d, J = 8.6 Hz, 1 H) 7.26 - 7.37 (m, 4 H) 7.43 - 7.45 (m, 1 H) 7.49 - 7.52 (m, 2 H) 7.55 (br t, J = 1.8 Hz, 1 H).

Ejemplo 3-27: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 2.07 (quinteto, J = 7.4 Hz, 2 H) 2.51 - 2.63 (m, 4 H) 2.82 - 3.02 (m, 8 H) 4.50 – 4.59 (m, 1 H) 6.28 (d, J = 8.6 Hz, 1 H) 6.78 - 6.81 (m, 1 H) 6.91 (d, J = 1.8 Hz, 1 H) 7.26 - 7.36 (m, 6 H) 7.41 - 7.44 (m, 1 H)

7.47 - 7.50 (m, 2 H) 7.53 - 7.54 (m, 1 H).

Ejemplo 3-28: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.24 (t, J = 7.2 Hz, 3 H) 2.44 - 2.69 (m, 6 H) 2.93 (A de ABX, J_{ab} = 13.7 Hz, J_{ax} = 7.8 Hz, 1 H) 3.00 (B de ABX, J_{ab} = 13.7 Hz, J_{bx} = 6.7 Hz, 1 H) 4.12 (q, J = 7.2 Hz, 2 H) 4.49 – 4.57 (m, 1 H) 6.35 (br d, J = 8.6 Hz, 1 H) 7.26 - 7.37 (m, 4 H) 7.43 - 7.46 (m, 1 H) 7.49 - 7.52 (m, 2 H) 7.55 (br t, J = 1.6 Hz, 1 H).

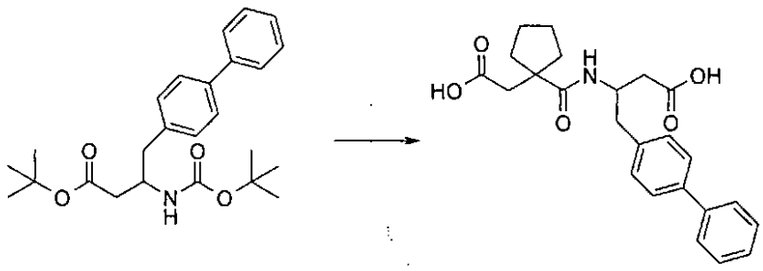
Ejemplo 3-29: Síntesis de ácido (R)-3-(4-(benciloxi)-4-oxo-butanamido)-4-(3'-cloro-bifenil-4-il)-butanoico



Una solución del mono-bencil-éster del ácido succínico (71.1 miligramos, 0.342 milimoles), EDCI (65.5 miligramos, 0.342 milimoles), y HOAt (46.5 miligramos, 0.342 milimoles) en N,N-dimetil-formamida (1 mililitro), la cual se deja agitándose a temperatura ambiente durante 1 hora, se agrega a una solución del ácido (R)-3-amino-4-(3'-cloro-bifenil-4-il)-butanoico (66 miligramos, 0.228 milimoles), y di-isopropil-etil-amina (0.080 mililitros, 0.456 milimoles) en un solvente mixto de dimetil-formamida (2 mililitros) y agua (2 mililitros). La mezcla de reacción se deja agitándose durante 3 horas, y entonces se diluye con H_2O. Los productos se extraen dos veces con EtOAc. La capa orgánica combinada se lava con salmuera,

se seca sobre Na_2SO_4, se filtra, y se concentra, para dar el producto crudo. El residuo resultante se purifica mediante HPLC de preparación utilizando un gradiente del 20 por ciento de MeCN/agua (ácido trifluoro-acético al 0.1 por ciento) al 100 por ciento de MeCN, para dar el ácido (R)-3-(4-(benciloxi)-4-oxo-butanamido)-4-(3'-cloro-bifenil-4-il)-butanoico (42.4 miligramos) como un sólido blanco; HPLC - tiempo de retención = 1.22 minutos (condición B); MS (m+1) = 480.35; ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 2.44 - 2.75 (m, 6 H) 2.86 - 2.99 (m, 2 H) 4.48 - 4.56 (m, 1 H) 5.11 (s, 2 H) 6.29 (br d, *J* = 8.6 Hz, 1 H) 6.97 - 7.07 (m, 10 H) 7.25 - 7.36 (m, 2 H) 7.42 - 7.50 (m, 2 H) 7.54 (br t, *J* = 1.6 Hz, 1 H).

Ejemplo 3-30: Síntesis de ácido 4-(bifenil-4-il)-3-(1-(carboxi-metil)-ciclopentan-carboxamido)-butanoico



Al 4-(bifenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoato de terbutilo (110 miligramos, 0.267 milimoles), se le agrega una solución de HCl 4M en 1,4-dioxano (0.668 mililitros, 2.67 milimoles). Después de agitar durante 1 hora, la mezcla de reacción se concentra, para dar el clorhidrato de terbutil-éster del ácido 3-amino-4-bifenil-4-il-butírico crudo.

En seguida, a una solución de EDCI (51.2 miligramos, 0.267

milimoles), 1-hidroxi-7-azabenzotriazol (36.4 miligramos, 0.267 milimoles), y una mezcla de 6 :1 de ácido 1-(2-(benciloxi)-2-oxo-etil)-ciclopentan-carboxílico y ácido 2-(1-(benciloxi-carbonil)-ciclopentil)-acético (65.6 miligramos, 0.214 milimoles) en N,N-dimetil-formamida (1 mililitro), la cual se agita durante 1.5 horas con anticipación, se le agregan el clorhidrato de terbutil-éster del ácido 3-amino-4-bifenil-4-il-butírico crudo y la di-isopropil-etil-amina (0.093 mililitros, 0.535 milimoles). Después de agitar durante 2.5 horas, la mezcla de reacción se diluye con H_2O, y los productos se extraen con EtOAc. La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea en gel de sílice (heptano/EtOAc = 100:0 a 0:100), para dar el 3-(1-(2-(benciloxi)-2-oxo-etil)-ciclopentan-carboxamido)-4-(bifenil-4-il)-butanoato de terbutilo crudo (38 miligramos).

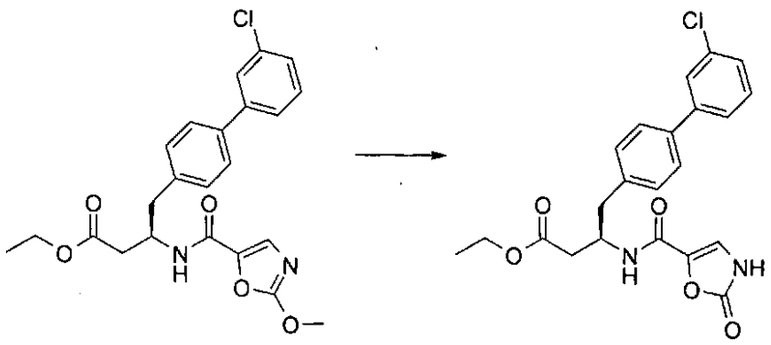
En seguida, a la solución del 3-(1-(2-(benciloxi)-2-oxo-etil)-ciclopentan-carboxamido)-4-(bifenil-4-il)-butanoato de terbutilo crudo (38 miligramos) en dicloro-metano (0.7 mililitros), se le agrega ácido trifluoro-acético (0.263 mililitros, 3.42 milimoles). Después de agitar durante 1 hora, la mezcla de reacción se concentra, para dar el ácido 3-(1-(2-(benciloxi)-2-oxo-etil)-ciclopentan-carboxamido)-4-(bifenil-4-il)-butanoico crudo (39 miligramos).

En seguida, una suspensión del producto crudo (39 miligramos), y Pd/C (16.6 miligramos, 7.8 micromoles) en EtOH (1 mililitro) se deja agitándose bajo hidrógeno a temperatura ambiente

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durante 4 horas. La mezcla de reacción se filtra y se concentra, para dar el producto crudo. El residuo resultante se purifica mediante HPLC de preparación utilizando un gradiente del 20 por ciento de MeCN/agua (ácido trifluoro-acético al 0.1 por ciento) al 100 por ciento de MeCN, para dar el ácido 4-(bifenil-4-il)-3-(1-(carboxi-metil)-ciclopentan-carboxamido)-butanoico (12.7 miligramos); HPLC - tiempo de retención = 1.16 minutos (condición B); MS (m+1) = 410.1; ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1.39 - 1.53 (m, 6 H) 1.83 - 1.98 (m, 2 H) 2.34 - 2.45 (m, 2 H) 2.53 (s, 2 H) 2.73 - 2.86 (m, 2 H) 4.21 - 4.33 (m, 1 H) 7.27 (d, *J* = 8.1 Hz, 2 H) 7.32 - 7.37 (m, 2 H) 7.43 - 7.46 (m, 2 H) 7.55 - 7.58 (m, 2 H) 7.62 - 7.64 (m, 2 H) 7.84 (br d, *J* = 8.9 Hz, 1 H).

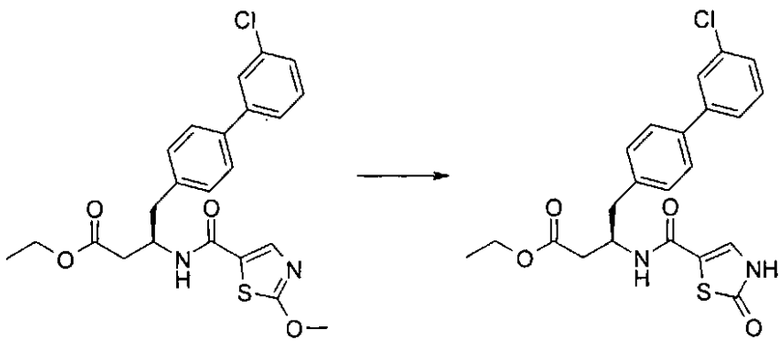
Ejemplo 3-31: Síntesis de 4-(3'-cloro-bifenil-4-il)-3-(2-oxo-2,3-dihidro-oxazol-5-carboxamido)-butanoato de (R)-etilo



A una solución de 4-(3'-cloro-bifenil-4-il)-3-(2-metoxi-oxazol-5-carboxamido)-butanoato de (R)-etilo, y el intermediario 14, (103 miligramos, 0.23 milimoles) en dioxano (3 mililitros), se le agrega una solución de HCl 4 N en dioxano (0.29 mililitros, 1.16 milimoles). El producto crudo se agita a temperatura ambiente durante 2 horas.

El producto crudo se concentra, y se diluye en agua y EtOAc. La capa orgánica se lava con salmuera, se seca sobre $MgSO_4$, se filtra, y se concentra. Se purifica el 50 por ciento del producto crudo por medio de HPLC en fase inversa (SunFire C18, H_2O (ácido trifluoro-acético al 0.1 por ciento)/CH_3CN), para dar el 4-(3'-cloro-bifenil-4-il)-3-(2-oxo-2,3-dihidro-oxazol-5-carboxamido)-butanoato de (R)-etilo (38 miligramos) como un sólido blanco. HPLC - tiempo de retención = 1.66 minutos (condición A); MS (m+1) = 429.4; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J*=7.1 Hz, 3 H) 2.51 - 2.69 (m, 2 H) 2.95 (dd, 1 H) 3.05 (dd, 1 H) 4.19 (q, 2 H) 4.58 - 4.75 (m, 1 H) 6.83 (d, *J*=8.8 Hz, 1 H) 7.26 - 7.33 (m, 4 H) 7.35 (t, *J*=7.7 Hz, 1 H) 7.45 (dt, *J*=7.6, 1.5 Hz, 1 H) 7.51 (d, *J*=8.3 Hz, 2 H) 7.56 (t, *J*=1.8 Hz, 1 H) 8.45 (br. s., 1 H).

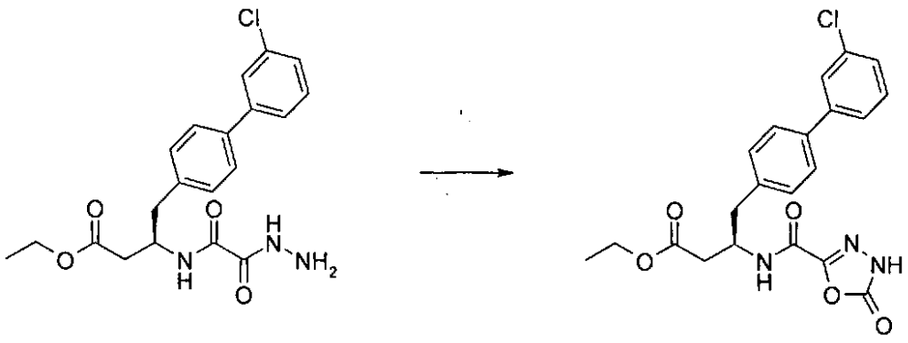
Ejemplo 3-32: Síntesis de 4-(3'-cloro-bifenil-4-il)-3-(2-oxo-2,3-dihidro-tiazol-5-carboxamido)-butanoato de (R)-etilo



A una solución de 4-(3'-cloro-bifenil-4-il)-3-(2-metoxi-tiazol-5-carboxamido)-butanoato de (R)-etilo, el intermediario 13, (170 miligramos, 0.37 milimoles) en dioxano (5 mililitros), se le agrega una solución de HCl 4M en dioxano (0.5 mililitros, 2.00 milimoles). El

producto crudo se agita a temperatura ambiente durante 3 horas. El producto crudo se concentra. Parte del producto crudo se purifica por medio de HPLC en fase inversa (SunFire C18, H_2O (ácido trifluoro-acético al 0.1 por ciento)/CH_3CN), para dar (95 miligramos) del 4-(3'-cloro-bifenil-4-il)-3-(2-oxo-2,3-dihidro-tiazol-5-carboxamido)-butanoato de (R)-etilo como un sólido blanco. HPLC - tiempo de retención = 1.82 minutos (condición D); MS (m+1) = 445.2. ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J*=7.1 Hz, 3 H) 2.46 - 2.70 (m, 2 H) 2.78-2.97 (m, 1 H) 3.07 (dd, *J*=13.0, 6.2 Hz, 1 H) 4.11 - 4.28 (m, 2 H) 4.51 - 4.69 (m, 1 H) 6.64 (d, *J*=8.1 Hz, 1H), 7.19-7.42 (m, 5 H) 7.44 (d, *J*=6.1 Hz, 1 H) 7.48-7.62 (m, 3H), 9.54 (br. s., 1 H).

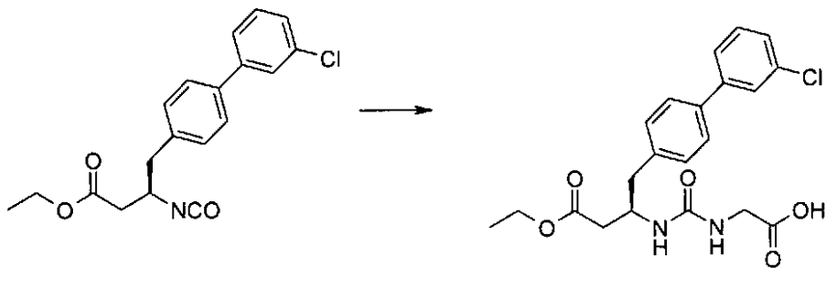
Ejemplo 3-33: Síntesis de 4-(3'-cloro-bifenil-4-il)-3-(5-oxo-4,5-dihidro-1,3,4-oxadiazol-2-carboxamido)-butanoato de (R)-etilo



A una solución de 4-(3'-cloro-bifenil-4-il)-3-(2-hidrazinil-2-oxo-acetamido)-butanoato de (R)-etilo, el intermediario 12, (289 miligramos, 0.72 milimoles) en tetrahidrofurano (8.5 mililitros), se le agrega 1,1'-carbonil-di-imidazol (139 miligramos, 0.86 milimoles) a temperatura ambiente. Después de agitar durante 18 horas a temperatura ambiente, la reacción se apaga con H_2O y HCl 1M, y el

producto crudo se diluye con EtOAc. La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante HPLC de fase inversa (SunFire C18, H_2O (ácido trifluoro-acético al 0.1 por ciento)/CH_3CN), y se liofiliza, para dar el 4-(3'-cloro-bifenil-4-il)-3-(5-oxo-4,5-dihidro-1,3,4-oxadiazol-2-carboxamido)-butanoato de (R)-etilo (100 miligramos). HPLC - tiempo de retención = 1.67 minutos (condición A); MS (m+1) = 430.2; ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.14 (t, *J*=7.1 Hz, 3 H) 2.52 - 2.70 (m, 2 H) 2.84 (dd, *J*=13.7, 8.4 Hz, 1 H) 2.90 (dd, *J*=13.7, 8.4 Hz, 1 H) 4.02 (q, *J*=7.1 Hz, 2 H) 4.42 - 4.58 (m, 1 H) 7.30 (d, *J*=8.1 Hz, 2 H) 7.37 - 7.43 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.57 - 7.66 (m, 3 H) 7.70 (t, *J*=1.9 Hz, 1 H) 8.98 (d, *J*=8.8 Hz, 1 H) 12.94 (s, 1 H).

Ejemplo 3-34: Síntesis de etil-éster del ácido (R)-3-(3-carboxi-metil-ureido)-4-(3'-cloro-bifenil-4-il)-butírico

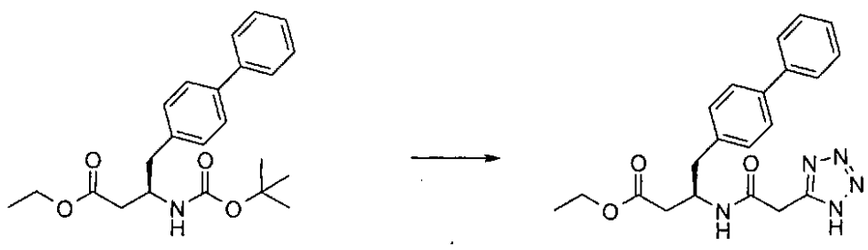


A una solución de 2-amino-acetato de terbutilo (19.08 miligramos, 0.145 milimoles), y DIEA (18.8 miligramos, 0.145 milimoles) en N,N-dimetil-formamida (1 mililitro), se le agrega el intermediario 45 (50 miligramos, 0.145 milimoles), y la mezcla se agita a temperatura ambiente durante 2 horas. El solvente se remueve bajo

presión reducida, para dar el etil-éster del ácido (R)-3-(3-terbutoxi-carbonil-metil-ureido)-4-(3'-cloro-bifenil-4-il)-butírico.

En seguida, a una solución del diéster anterior (70 miligramos, 0.147 milimoles) en cloruro de metileno (2 mililitros), se le agrega ácido trifluoro-acético (4 mililitros), y la mezcla se agita a temperatura ambiente durante 18 horas. Los solventes se remueven bajo presión reducida, y el residuo se purifica mediante HPLC de preparación utilizando un gradiente del 35 por ciento de MeCN/agua al 100 por ciento de MeCN (+ ácido trifluoro-acético al 0.1 por ciento). La liofilización de las fracciones apropiadas da el compuesto del título; HPLC - tiempo de retención 1.42 minutos (condición C); MS 419.1 (M+1); ^{1}H RMN (400 MHz, DMSO-d6): δ ppm 1.17 (t, J=7.07 Hz, 3H), 2.41 (d, J=7.07 Hz, 2H), 2.77-2.79 (m, 2H), 3.66-3.68 (m, 2H), 4.04 (q, J=7.07 Hz, 2H), 4.08-4.15 (m, 1H), 6.13 (t, J=5.81 Hz, 1H), 6.24 (d, J=8.59 Hz, 1H), 7.28-7.30 (m, 2H), 7.39-7.42 (m, 1H), 7.48 (t, J = 7.83 Hz, 1H), 7.62-7.64 (m, 3H), 7.71 (t, J=1.77 Hz, 1H), 12.42 (s, 1H).

Ejemplo 4-1: Síntesis de etil-éster del ácido (R)-4-bifenil-4-il-3-(2-1H-tetrazol-5-il-acetil-amino)-butírico



Intermediario 2

A una solución del etil-éster del ácido (R)-4-bifenil-4-il-3-

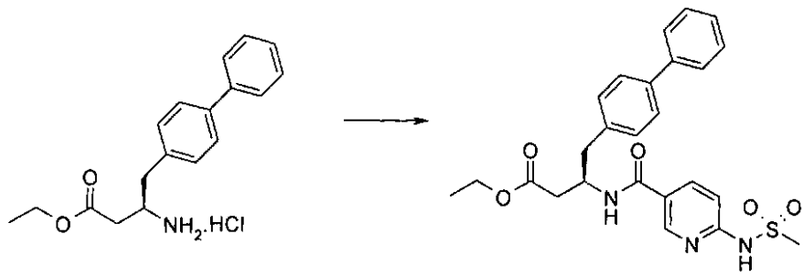
terbutoxi-carbonil-amino-butírico (100 miligramos, 0.261 milimoles) en dicloro-metano (3 mililitros) a temperatura ambiente, se le agrega ácido trifluoro-acético (1 mililitro, 12.98 milimoles), y la mezcla se agita a temperatura ambiente durante 0.5 horas. La mezcla se concentra bajo presión reducida, para dar la sal de ácido trifluoro-acético del etil-éster del ácido (R)-3-amino-4-bifenil-4-il-butírico. HPLC - tiempo de retención = 1.50 minutos (condición C); MS (m+1) = 384.

En seguida, a una suspensión de la sal de ácido trifluoro-acético del etil-éster del ácido (R)-3-amino-4-bifenil-4-il-butírico (0.074 gramos, 0.261 milimoles) en dicloro-metano (10 mililitros) a temperatura ambiente, se le agregan ácido 1H-tetrazol-5-acético (0.050 gramos, 0.392 milimoles). A la mezcla a una temperatura del baño helada, se le agrega cloruro bis-(2-oxo-3-oxazolidinil)-fosfínico (0.100 gramos, 0.392 milimoles), y rápidamente es seguido por di-isopropil-etil-amina (0.137 mililitros, 0.783 milimoles). La mezcla de reacción se calienta lentamente hasta la temperatura ambiente, y se agita durante la noche. La reacción se extrae con dicloro-metano. La capa orgánica combinada se lava con $NaHCO_3$ saturado, NH_4Cl saturado, salmuera, y se seca sobre sulfato de sodio anhidro, se filtra, y se concentra bajo presión reducida, para dar el etil-éster del ácido (R)-4-bifenil-4-il-3-(2-1H-tetrazol-5-il-acetil-amino)-butírico. HPLC - tiempo de retención = 1.04 minutos (condición E); MS (m+1) = 394.

Ejemplo 4-2: Síntesis de 4-(bifenil-4-il)-3-(6-(metil-

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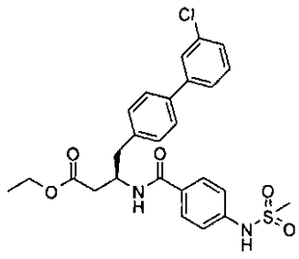
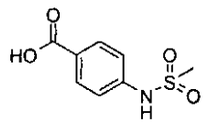
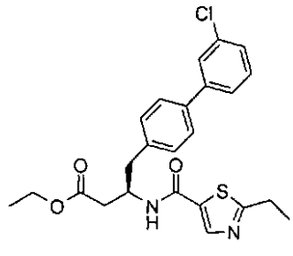
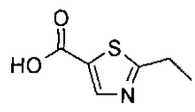
sulfonamido)-nicotinamido)-butanoato de (R)-etilo

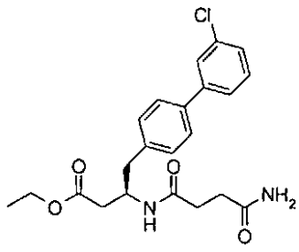
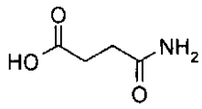
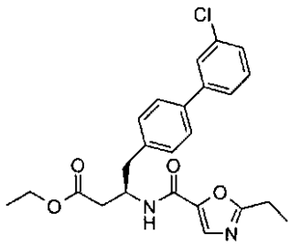
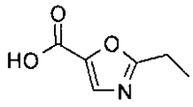


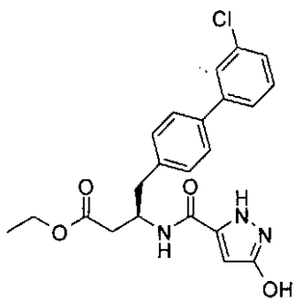
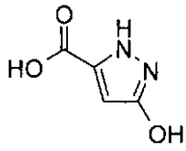
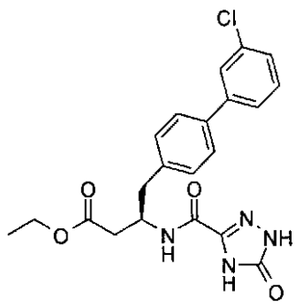
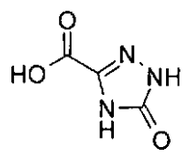
A una solución de clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-etilo (103 miligramos, 0.32 milimoles), y ácido 6-(metil-sulfonamido)-nicotínico, el intermediario 15 (84 miligramos, 0.39 milimoles) en CH_2Cl_2 (2 mililitros) y dimetil-formamida (2 mililitros), se le agregan trietil-amina (0.18 mililitros, 1.29 milimoles), y HATU (159 miligramos, 0.42 milimoles), a temperatura ambiente. El producto crudo se agita a temperatura ambiente durante 2 horas. El producto crudo se apaga con $NaHCO_3$ saturado, y se diluye en EtOAc. La capa orgánica se lava seis veces con agua, salmuera, se seca sobre $MgSO_4$, se filtra, y se concentra. El producto crudo se purifica por medio de HPLC en fase inversa (SunFire C18, H_2O (ácido trifluoro-acético al 0.1 por ciento)/CH_3CN), para dar el 4-(bifenil-4-il)-3-(6-(metil-sulfonamido)-nicotinamido)-butanoato de (R)-etilo como un sólido blanco (4.1 miligramos). HPLC - tiempo de retención = 1.61 minutos (condición A); MS (m+1) = 482.3. ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.22 (t, *J*=7.2 Hz, 3 H), 2.56 (t, *J*=4.8 Hz, 2 H), 2.84 - 2.92 (m, 1 H), 3.05 (dd, *J*=13.6, 6.1 Hz, 1 H), 3.16 (s, 3 H), 4.08 - 4.18 (m, 2 H), 4.57 - 4.71 (m, 1 H), 7.03 (d, *J*=8.3 Hz, 1 H), 7.10 (d, *J*=8.3 Hz, 1 H), 7.22 (d, *J*=8.3 Hz, 2 H), 7.26

- 7.31 (m, 1 H), 7.33 - 7.40 (m, 2 H), 7.44 - 7.54 (m, 5 H), 7.98 (dd, *J*=8.8, 2.3 Hz, 1 H), 8.52 (s, 1 H).

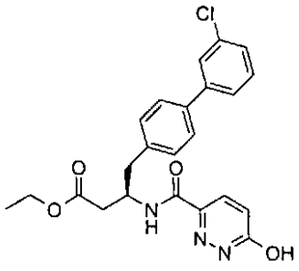
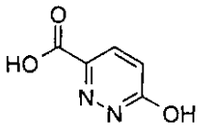
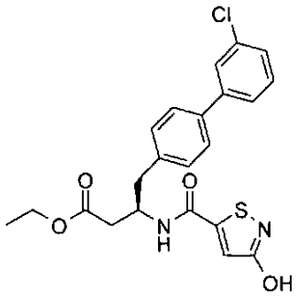
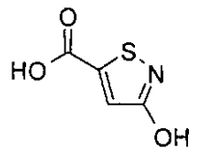
Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 4-2:

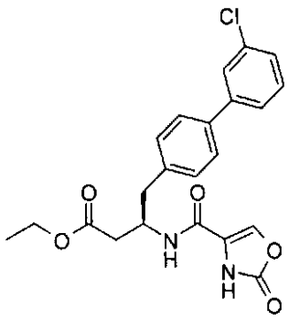
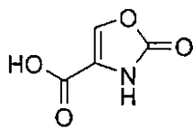
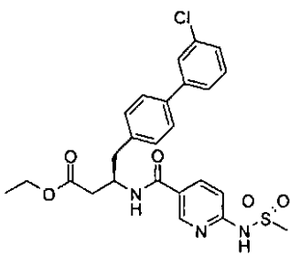
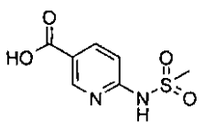
Ejemplo #	Producto	Reactivo	LCMS-RT (condición)	MS (M+1)
Ejemplo 4-3	 4-(3'-cloro-bifenil-4-il)-3-(4-(metil-sulfonamido)benzamido)-butanoato de (R)-etilo	 EDCI y HOAt usados en lugar de HATU	1.68 min (A)	515.2
Ejemplo 4-4	 4-(3'-cloro-bifenil-4-il)-3-(2-etil-tiazol-5-carboxamido)-	 intermediario 26	1.63 min (A)	457.2

Ejemplo #	Producto	Reactivo	LCMS-RT (condición)	MS (M+1)
	butanoato de (R)-etilo			
Ejemplo 4-5	 3-(4-amino-4-oxo-butanamido)-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-etilo	 EDCI y HOAt usados en lugar de HATU	1.49 min (A)	417.3
Ejemplo 4-6	 4-(3'-cloro-bifenil-4-il)-3-(2-etil-oxazol-5-carboxamido)-butanoato de (R)-etilo	 intermediario 23	1.60 min (A)	441.3

Ejemplo #	Producto	Reactivo	LCMS-RT (condición)	MS (M+1)
Ejemplo 4-7	 4-(3'-cloro-bifenil-4-il)-3-(3-hidroxi-1H-pirazol-5-carboxamido)-butanoato de (R)-etilo		1.82 min (A)	428.2
Ejemplo 4-8	 4-(3'-cloro-bifenil-4-il)-3-(5-oxo-4,5-dihidro-1H-1,2,4-triazol-3-carboxamido)-	 EDCI y HOAt usados en lugar de HATU	1.86 min (D)	429.2

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Ejemplo #	Producto	Reactivo	LCMS-RT (condición)	MS (M+1)
	butanoato de (R)-etilo			
Ejemplo 4-9	 4-(3'-cloro-bifenil-4-il)-3-(6-hidroxi-piridazin-3-carboxamido)-butanoato de (R)-etilo	 EDCI y HOAt usados en lugar de HATU	1.82 min (D)	440.2
Ejemplo 4-10	 4-(3'-cloro-bifenil-4-il)-3-(3-hidroxi-isotiazol-5-	 intermediario 20 EDCI y HOAt usados en lugar de	1.56 min (A)	445.3

Ejemplo #	Producto	Reactivo	LCMS-RT (condición)	MS (M+1)
	carboxamido)-butanoato de (R)-etilo	HATU		
Ejemplo 4-11	 4-(3'-cloro-bifenil-4-il)-3-(2-oxo-2,3-dihidro-oxazol-4-carboxamido)-butanoato de (R)-etilo	 Intermediario 19 EDCI y HOAt usados en lugar de HATU	1.79 min (D)	429.1
Ejemplo 4-12	 4-(3'-cloro-bifenil-4-il)-3-(6-(metil-	 intermediario 15	1.81 minutos. (D)	516.2

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Ejemplo #	Producto	Reactivo	LCMS-RT (condición)	MS (M+1)
	sulfonamido)-nicotinamido)-butanoato de (R)-etilo			

Ejemplo 4-3: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.1 Hz, 3 H) 2.52 - 2.67 (m, 2 H) 2.88 (dd, *J*=13.3, 8.0 Hz, 1 H) 2.95 (dd, *J*=13.3, 8.0 Hz, 1 H) 3.05 (s, 3 H) 4.02 (q, *J*=7.1 Hz, 2 H) 4.46 - 4.65 (m, 1 H) 7.23 (d, *J*=8.8 Hz, 2 H) 7.34 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.59 - 7.66 (m, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 7.75 (d, *J*=8.6 Hz, 2 H) 8.31 (d, *J*=8.3 Hz, 1 H) 10.07 (s, 1 H)

Ejemplo 4-4: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.1 Hz, 3 H) 1.28 (t, *J*=7.5 Hz, 3 H) 2.59 (d, *J*=7.1 Hz, 2 H) 2.81 - 2.94 (m, 2 H) 2.97 (q, *J*=7.6 Hz, 2 H) 4.03 (q, *J*=7.1 Hz, 2 H) 4.40 - 4.55 (m, 1 H) 7.32 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.58 - 7.65 (m, 3 H) 7.69 (t, *J*=1.9 Hz, 1 H) 8.18 (s, 1 H) 8.52 (d, *J*=8.3 Hz, 1 H)

Ejemplo 4-5: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.24 (t, *J*=7.1 Hz, 3 H) 2.38 - 2.60 (m, 6 H) 2.78 - 2.94 (m, 2 H) 4.10 (q, *J*=7.1 Hz, 2 H) 4.42 - 4.55 (m, 1 H) 7.32 (d, *J*=8.3 Hz, 2 H) 7.40 (t, *J*=7.83 Hz, 1 H) 7.50 - 7.53 (m, 4 H) 7.60 (t, *J*=1.89 Hz, 1 H)

Ejemplo 4-6: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.2 Hz, 3 H) 1.25 (t, *J*=7.6 Hz, 3 H) 2.53 - 2.65 (m, 2 H) 2.80 (q, *J*=7.6 Hz, 2 H) 2.84 - 2.96 (m, 2 H) 4.02 (q, *J*=7.1 Hz, 2 H) 4.42 - 4.60 (m, 1 H) 7.31 (d, *J*=8.3 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.59 (s, 1 H) 7.60 - 7.65 (m, 3 H) 7.69 (t, *J*=1.9 Hz, 1 H) 8.48 (d, *J*=8.6 Hz, 1 H)

Ejemplo 4-7: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.1 Hz, 3 H) 2.52 - 2.65 (m, 2 H) 2.85 (dd, *J*=13.6, 5.8 Hz, 1 H) 2.91 (dd, *J*=13.6, 5.8 Hz, 1 H) 4.02 (q, *J*=7.1 Hz, 2 H) 4.38 - 4.60 (m, 1 H) 5.89 (s, 1 H) 7.31 (d, *J*=8.3 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.58 - 7.65 (m, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 8.10 (d, *J* = 8.6 Hz, 1 H)

Ejemplo 4-8: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.22 (t, *J*=7.2 Hz, 3 H) 2.56 - 2.72 (m, 2 H) 2.95 (d, *J*=7.3 Hz, 2 H) 4.11 (q, *J*=7.2 Hz, 2 H) 4.53 - 4.73 (m, 1 H) 7.28 - 7.36 (m, 3 H) 7.39 (t, *J*=7.8 Hz, 1 H) 7.48 - 7.55 (m, 3 H) 7.58 (t, *J*=1.8 Hz, 1 H)

Ejemplo 4-9: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.1 Hz, 3 H) 2.53 - 2.71 (m, 2 H) 2.85 (dd, *J*=13.7, 8.3 Hz, 1 H) 2.96 (dd, *J*=13.7, 8.3 Hz, 1 H) 4.02 (q, *J*=7.1 Hz, 2 H) 4.45 - 4.63 (m, 1 H) 6.93 (dd, *J*=9.9, 2.3 Hz, 1 H) 7.30 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.42 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.61 (d, *J*=8.3 Hz, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 7.75 (d, *J* = 9.9 Hz, 1 H) 8.45 (d, *J* = 9.1 Hz, 1 H) 13.41 (d, *J* = 2.0 Hz, 1 H)

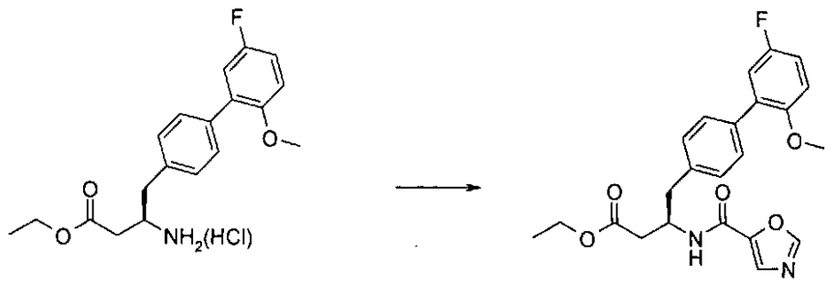
Ejemplo 4-10: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.1 Hz, 3 H) 2.60 (d, *J*=7.6 Hz, 2 H) 2.90 (d, *J*=6.8 Hz, 2 H) 4.02 (q,

J=7.2 Hz, 2 H) 4.39 - 4.53 (m, 1 H) 7.11 (s, 1 H) 7.32 (d, *J*=8.1 Hz, 2 H) 7.37 - 7.43 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.60 - 7.66 (m, 3 H) 7.70 (t, *J*=1.9 Hz, 1 H) 8.72 (d, *J*=8.3 Hz, 1 H) 11.76 (br. s., 1 H)

Ejemplo 4-11: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.27 (t, *J*=7.1 Hz, 3 H) 2.47 - 2.69 (m, 2 H) 2.90 (dd, *J*=13.6, 7.8 Hz, 1 H) 3.06 (dd, *J*=13.6, 6.6 Hz, 1 H) 3.06 (amplia s, 1H) 4.07 - 4.28 (m, 2 H) 4.52 - 4.74 (m, 1 H) 7.21 - 7.37 (m, 5 H) 7.38 - 7.44 (m, 1 H) 7.48 (d, *J*=8.1 Hz, 2 H) 7.53 (t, *J*=1.6 Hz, 1 H) 9.50 (br. s., 1 H).

Ejemplo 4-12: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.1 Hz, 3 H) 2.59 (d, *J*=7.3 Hz, 2 H) 2.76 - 3.03 (m, 2 H) 4.03 (q, *J*=7.1 Hz, 2 H) 4.39 - 4.66 (m, 1 H) 7.02 (d, 1 H) 7.28 - 7.54 (m, 4 H) 7.54 - 7.80 (m, 4 H) 8.05 (dd, *J*=8.6, 2.3 Hz, 1 H) 8.45 (d, *J*=8.3 Hz, 1 H) 8.61 (br. s., 1 H).

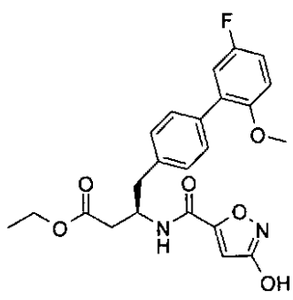
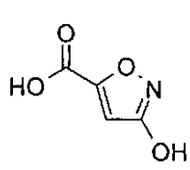
Ejemplo 4-13: Síntesis de 4-(5'-fluoro-2'-metoxi-bifenil-4-il)-3-(oxazol-5-carboxamido)-butanoato de (R)-etilo



A una solución de ácido oxazol-5-carboxílico (70 miligramos, 0.61 milimoles) en N,N-dimetil-formamida (1.5 mililitros), y dicloro-metano (1.5 mililitros), se le agrega clorhidrato de 3-amino-4-(5'-fluoro-2'-metoxi-bifenil-4-il)-butanoato de (R)-etilo, el intermediario 10, (150 miligramos, 0.41 milimoles), HATU (233 miligramos, 0.61

milimoles), y trietil-amina (284 microlitros, 2.04 milimoles). Después de agitar durante 2 horas, la reacción se apaga con H_2O, y el producto crudo se diluye con EtOAc, la capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante HPLC de fase inversa (SunFire C18, H_2O (ácido trifluoro-acético al 0.1 por ciento)/CH_3CN), y se liofiliza, para dar el 4-(5'-fluoro-2'-metoxi-bifenil-4-il)-3-(oxazol-5-carboxamido)-butanoato de (R)-etilo (157 miligramos). HPLC - tiempo de retención = 1.50 minutos (condición A); MS (m+1) = 427.4; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.19 (t, *J*=7.2 Hz, 3 H) 2.46 - 2.62 (m, 2 H) 2.86 (dd, *J*=13.6, 8.1 Hz, 1 H) 3.02 (dd, *J*=13.6, 6.1 Hz, 1 H) 3.67 (s, 3 H) 4.05 - 4.15 (m, 2 H) 4.52 - 4.69 (m, 1 H) 6.76 - 6.82 (m, 1 H) 6.83 - 6.96 (m, 2 H) 7.11 - 7.21 (m, 3 H) 7.37 (d, *J*=8.1 Hz, 2 H) 7.61 (s, 1 H) 7.80 (s, 1 H)

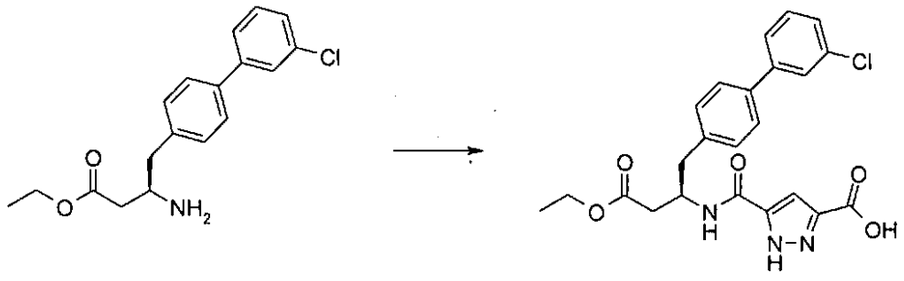
Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 4-13:

Ejemplo #	Producto	Reactivo	LCMS-RT (condición)	MS (M+1)
Ejemplo 4-14			1.43 minutos. (A)	443.3

Ejemplo #	Producto	Reactivo	LCMS-RT (condición)	MS (M+1)
	4-(5'-fluoro-2'-metoxi-bifenil-4-il)-3-(3-hidroxi-isoxazol-5-carboxamido)-butanoato de (R)-etilo			

Ejemplo 4-14: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.21 (t, *J*=7.1 Hz, 3 H) 2.61 - 2.68 (m, 2 H) 2.95 (d, *J*=7.1 Hz, 2 H) 3.74 (s, 3 H) 4.10 (q, *J*=7.1 Hz, 2 H) 4.60 - 4.73 (m, 1 H) 6.43 (s, 1 H) 6.98 - 7.06 (m, 3 H) 7.27 (d, *J* = 8.1 Hz, 2 H) 7.38 - 7.48 (m, 2 H) 8.78 (d, *J* = 8.8 Hz, 1 H)

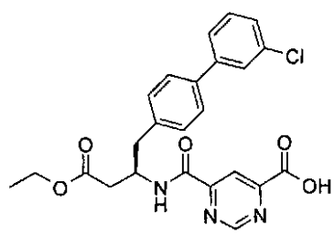
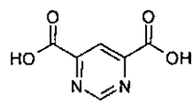
Ejemplo 4-15: Síntesis de ácido 5-[(R)-1-(3'-cloro-bifenil-4-il-metil)-2-etoxi-carbonil-etil-carbamoil]-1H-pirazol-3-carboxílico



A una mezcla del intermediario 17-1 (130 miligramos, 0.367 milimoles), ácido 1H-pirazol-3,5-dicarboxílico (74.5 miligramos, 0.477

milimoles), EDCI (91 miligramos, 0.477 milimoles), y HOBt (64.5 miligramos, 0.477 milimoles) en N,N-dimetil-formamida (3 mililitros), se le agrega trietil-amina (149 miligramos, 0.203 milimoles), y la mezcla se agita a temperatura ambiente durante 18 horas. Cualquier material insoluble se remueve mediante filtración, y el filtrado se pasa por cromatografía mediante HPLC utilizando un gradiente desde el 10 por ciento de MeCN/agua hasta el 100 por ciento de MeCN (+ ácido trifluoro-acético al 0.1 por ciento). La liofilización de las fracciones apropiadas da el compuesto del título; HPLC - tiempo de retención 1.31 minutos (condición C); MS 456.2 (M+1); ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1.12 (t, J=7.07 Hz, 3H), 2.54-2.67 (m, 2H), 2.84-2.97 (m, 2H), 4.02 (q, J=7.07 Hz, 2H), 4.54 (m, 1H), 7.11 (s, amplia, 1H), 7.32 (d, J=8.08 Hz, 2H), 7.39 (m, 1H), 7.46 (t, 1H), 7.62 (d, J=8.08 Hz, 3H), 7.69 (s, 1H), 8.41 (s, amplia, 1H).

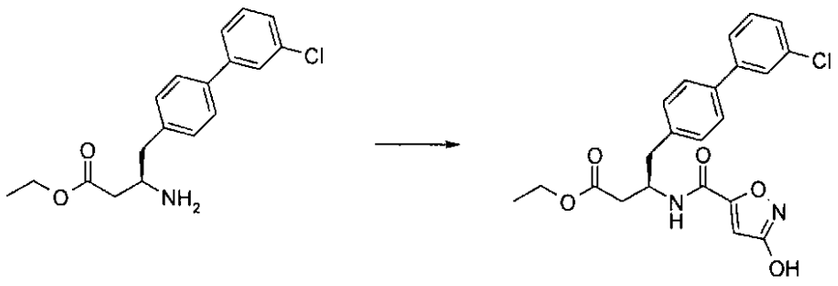
Se preparan los siguientes compuestos empleando el procedimiento descrito para el Ejemplo 4-15.

Ejemplo #	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
Ejemplo 4-16	 ácido 6-[(R)-1-(3'-		1.31 minutos. (C)	468.2

Ejemplo #	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
	cloro-bifenil-4-il-metil)-2-etoxi-carbonil-etil-carbamoil]-pirimidin-4-carboxílico			

Ejemplo 4-16: ^{1}H RMN (400 MHz, DMSO-d6): δ ppm 1.11 (t, J=7.07 Hz, 3H), 2.59-2.79 (m, 2H), 2.87-2.92 (m, 1H), 2.98-3.04 (m, 1H), 4.01 (q, J=7.33 Hz, 2H), 4.57-4.66 (m, 1H), 7.30-7.32 (m, 2H), 7.37-7.40 (m,1H), 7.45 (t, J=7.58 Hz, 1H), 7.59-7.61 (m, 3H), 7.68 (t, J=1.77 Hz, 1H), 8.16 (s, 1H), 9.10 (d, J=9.35 Hz, 1H), 9.31 (s, 1H).

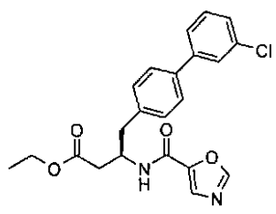
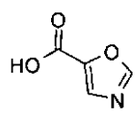
Ejemplo 4-17: Etil-éster del ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(3-hidroxi-isoxazol-5-carbonil)-amino]-butírico

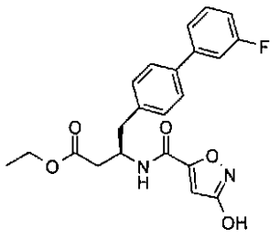
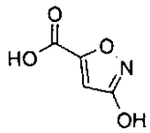


A una solución del intermediario 16-1 (40.6 miligramos, 0.315 milimoles), y HATU (144 miligramos, 0.378 milimoles) en N,N-dimetil-formamida (2 mililitros), se le agrega piridina (74.7 miligramos, 0.76 mililitros, 0.944 milimoles), y la mezcla se agita a temperatura

ambiente durante 15 minutos. Entonces se agrega el intermediario 17-1, y la agitación se continúa durante 2 horas. Cualquier material insoluble se remueve mediante filtración, y el filtrado se pasa por cromatografía mediante HPLC utilizando un gradiente desde el 10 por ciento de MeCN/agua hasta el 100 por ciento de MeCN (+ ácido trifluoro-acético al 0.1 por ciento). La liofilización de las fracciones apropiadas da el compuesto del título. HPLC - tiempo de retención 1.36 minutos (condición C); MS 429.1 (M+1); ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1.13 (t, J=7.07 Hz, 3 H) 2.60 (dd, J=6.95, 3.66 Hz, 2 H) 2.81 - 2.95 (m, 2 H) 4.02 (q, J=7.24 Hz, 2 H) 4.49 (d, J=7.83 Hz, 1 H) 6.49 (s, 1 H) 7.31 (d, J=8.34 Hz, 2 H) 7.37 - 7.43 (m, 1 H) 7.47 (t, J=7.83 Hz, 1 H) 7.59 - 7.66 (m, 3 H) 7.70 (t, J=1.89 Hz, 1 H) 8.83 (d, J=8.84 Hz, 1 H).

Se preparan los siguientes compuestos empleando el procedimiento descrito para el Ejemplo 4-17

Ejemplo #	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
Ejemplo 4-18	 etil-éster del ácido (R)-4-(3'-cloro-bifenil-4-il)-3-		1.48 minutos. (C)	413.1

Ejemplo #	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
	[(oxazol-5-carbonil)-amino]-butírico			
Ejemplo 4-19	 etil-éster del ácido (R)-4-(3'-fluoro-bifenil-4-il)-3-[(3-hidroxi-isoxazol-5-carbonil)-amino]-butírico		1.22 minutos. (C)	413.1

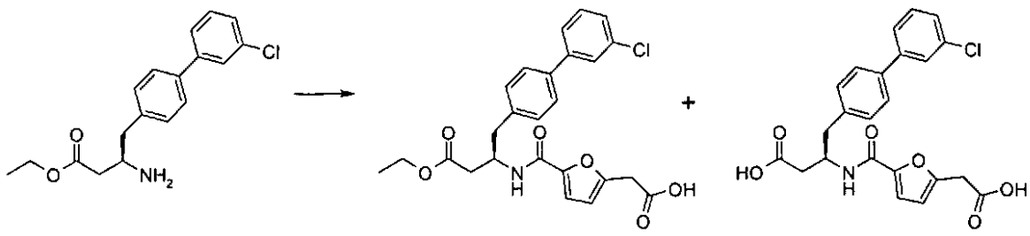
Ejemplo 4-18: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1.12 (t, J=7.07 Hz, 3 H) 2.60 (dd, J=6.95, 2.65 Hz, 2 H) 2.82 - 2.96 (m, 2 H) 4.02 (q, J=7.07 Hz, 2 H) 4.45 - 4.58 (m, 1 H) 7.31 (d, J=8.34 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 (t, J=7.83 Hz, 1 H) 7.58 - 7.65 (m, 3 H) 7.69 (t, J=1.77 Hz, 1 H) 7.72 (s, 1 H) 8.55 (s, 1 H) 8.63 (d, J=8.59 Hz, 1 H).

Ejemplo 4-19: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.07 Hz, 3 H) 2.54 - 2.75 (m, 2 H) 2.76 - 3.02 (m, 2 H) 4.02 (q, *J*=7.07 Hz, 2 H) 4.29 - 4.70 (m, 1 H) 6.49 (s, 1 H) 6.96 - 7.23 (m, 1 H) 7.30 (d,

J=8.08 Hz, 2 H) 7.44 - 7.58 (m, 3 H) 7.64 (d, *J*=8.08 Hz, 2 H) 8.83 (d, *J*=8.59 Hz, 1 H) 11.68 (s, 1 H).

Ejemplo 4-20: Etil-éster del ácido (R)-3-[(5-carboxi-metil-furan-2-carbonil)-amino]-4-(3'-cloro-bifenil-4-il)-butírico y

Ejemplo 4-21: Ácido (R)-3-[(5-carboxi-metil-furan-2-carbonil)-amino]-4-(3'-cloro-bifenil-4-il)-butírico



La reacción se lleva a cabo de una manera similar al Ejemplo 4-15 utilizando el intermediario 16-1 y el intermediario 44, para dar el etil-éster del ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(5-metoxi-carbonil-metil-furan-2-carbonil)-amino]-butírico. HPLC - tiempo de retención 1.38 minutos (condición C).

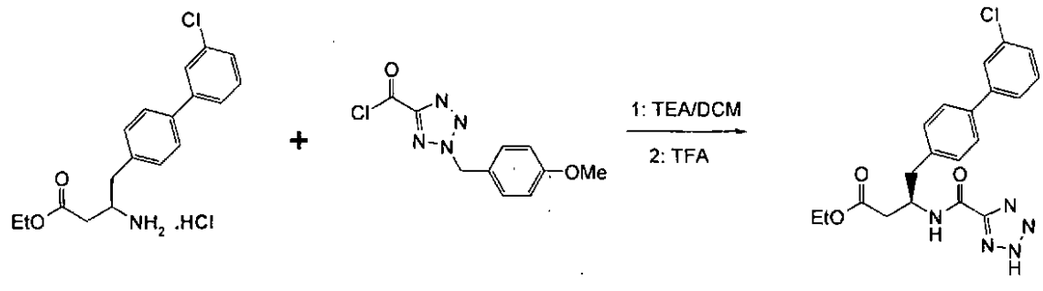
En seguida, a una solución del diéster anterior (235 miligramos, 0.486 milimoles) en EtOH (5 mililitros), se le agrega NaOH 1N (0.486 mililitros), y la mezcla se agita a temperatura ambiente durante 4 horas. El solvente se remueve bajo presión reducida, y se agrega agua (4 mililitros). La solución se acidifica con HCl 1N, y la mezcla se extrae con EtOAc. La fase orgánica se seca sobre sulfato de sodio, y el solvente se remueve bajo presión reducida. El residuo se purifica mediante HPLC de preparación utilizando un gradiente desde el 10 por ciento de MeCN/agua hasta

el 100 por ciento de MeCN (+ ácido trifluoro-acético al 0.1 por ciento). La liofilización de las fracciones apropiadas da los compuestos del título.

Etil-éster del ácido (R)-3-[(5-carboxi-metil-furan-2-carbonil)-amino]-4-(3'-cloro-bifenil-4-il)-butírico. HPLC - tiempo de retención 1.35 minutos (condición C); MS 470.0 (M+1); ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1.13 (t, J= 7.07 Hz, 3H), 2.50-2.64 (m, 2H), 2.81-2.95 (m, 2H), 3.74 (s, 2H), 4.01 (q, J=7.07 Hz, 2H), 4.51 (m, 1H), 6.99 (d, J=3.28 Hz, 1H), 7.31 (d, J=8.34 Hz, 2H), 7.38-7.41 (m, 1H), 7.47 (t, 1H), 7.62 (d, J=8.08 Hz, 3H), 7.69 (t, 1H), 8.24 (d, J=8.84 Hz, 1H).

Ácido (R)-3-[(5-carboxi-metil-furan-2-carbonil)-amino]-4-(3'-cloro-bifenil-4-il)-butírico. HPLC - tiempo de retención 0.94 minutos (condición C); MS 442.0 (M+1); ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.44-2.58 (m, 2H), 2.81-2.94 (m, 2H), 3.74 (s, 2H), 4.48 (m, 1H), 6.39 (d, J=3.28 Hz, 1H),6.99 (d, J=3.54 Hz, 1H), 7.30 (d, J=8.34 Hz, 2H), 7.38-7.41 (m, 1H), 7.47 (t, 1H), 7.62 (d, J=8.34 Hz, 3H), 7.70 (t, J=1.77 Hz,1H), 8.22 (d, J=8.84 Hz, 1H).

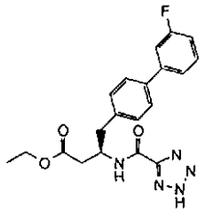
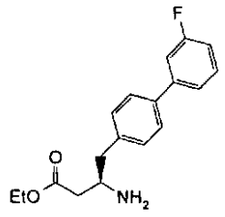
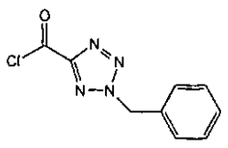
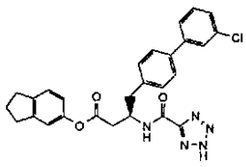
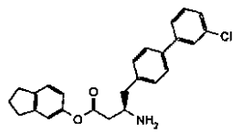
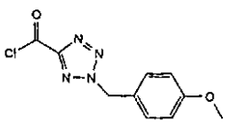
Ejemplo 4-22: Etil-éster del ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(2H-tetrazol-5-carbonil)-amino]-butírico



A una solución del intermediario 16-1 en dicloro-metano (8 mililitros) a temperatura ambiente, se le agrega cloruro de 2-(4-metoxi-bencil)-2H-tetrazol-5-carbonilo, seguido por trietil-amina (0.293 mililitros, 2.100 milimoles). La reacción se agita a temperatura ambiente durante 5 minutos. La reacción se apaga con salmuera, y se extrae con dicloro-metano. La capa orgánica combinada se lava con salmuera, y se seca sobre sulfato de sodio anhidro, se filtra, y se concentra bajo presión reducida. El residuo se purifica mediante cromatografía en columna (del 15 por ciento al 40 por ciento de EtOAc/Heptano). El residuo obtenido en ácido trifluoro-acético (5 mililitros, 64.9 milimoles) se calienta a 80°C durante 0.5 horas. La reacción se concentra bajo presión reducida, para dar el etil-éster del ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(2H-tetrazol-5-carbonil)-amino]-butírico.

HPLC - tiempo de retención = 1.31 minutos (condición B); MS (m+1) = 414.1; ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.11 (t, J=7.1 Hz, 3 H), 2.63 (dd, J=15.4, 5.6 Hz, 1 H), 2.72 (dd, J=15.4, 8.3 Hz, 1 H), 2.86 - 2.99 (m, 2 H), 4.02 (q, J=7.1 Hz, 2 H), 4.55 - 4.67 (m, 1 H), 7.32 (d, J=8.1 Hz, 2 H), 7.37 - 7.42 (m, 1 H), 7.46 (t, J=7.8 Hz, 1 H), 7.60 (d, J=8.1 Hz, 3 H), 7.68 (t, J=1.8 Hz, 1 H), 9.37 (d, J=8.8 Hz, 1 H).

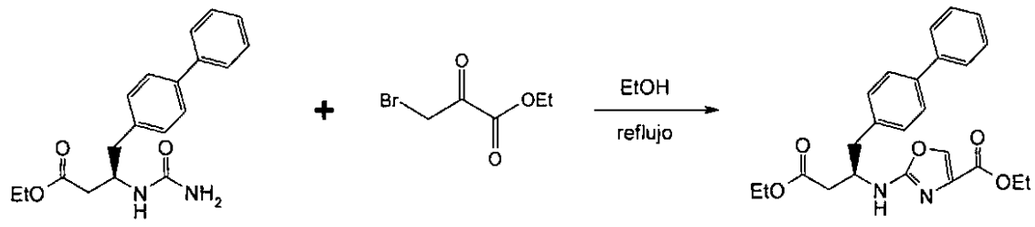
Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 4-22:

Ejemplo #	Producto	Material de partida	Condición de Desprotección	HPLC-RT (condición)	MS (M+1)
Ejemplo 4-23	 etil-éster del ácido (R)-4-(3'-fluoro-bifenil-4-il)-3-[(2H-tetrazol-5-carbonil)-amino]-butírico	 	1 atm. H_2, 10% Pd/C, EtOH, RT	1.12 minutos. (B)	398.2
Ejemplo 4-24	 indan-5-il-éster del ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(2H-tetrazol-5-carbonil)-amino]-butírico	 	TFA, 80°C	1.68 minutos. (B)	502.3

Ejemplo 4-23: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.12 (t, J=7.2 Hz, 3 H), 2.59 - 2.67 (m, J=15.4, 5.6 Hz, 1 H), 2.72 (dd, J=15.4, 8.3 Hz, 1 H), 2.85 - 3.01 (m, 2 H), 4.02 (q, J=7.1 Hz, 2 H), 4.55 - 4.67 (m, 1 H), 7.11 - 7.19 (m, 1 H), 7.32 (d, J=8.3 Hz, 2 H), 7.42 - 7.51 (m, 3 H), 7.61 (d, J=8.3 Hz, 2 H), 9.34 (d, J=8.8 Hz, 1 H).

Ejemplo 4-24: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.95 - 2.06 (m, 2 H), 2.75 - 2.92 (m, 6 H), 2.95 (dd, J=13.5, 5.9 Hz, 1 H), 3.06 (dd, J=13.6, 8.1 Hz, 1 H), 4.64 - 4.76 (m, 1 H), 6.78 (dd, J=8.1, 2.3 Hz, 1 H), 6.88 (d, J=1.5 Hz, 1 H), 7.17 (d, J=8.1 Hz, 1 H), 7.34 - 7.41 (m, 3 H), 7.46 (t, J=7.8 Hz, 1 H), 7.59 - 7.65 (m, 3 H), 7.70 (t, J=1.8 Hz, 1 H), 8.43 (d, J=8.8 Hz, 1 H).

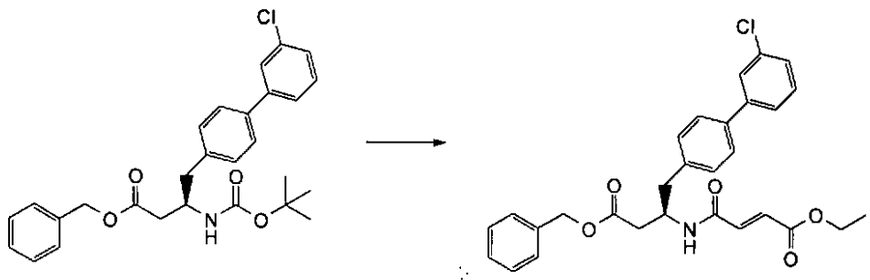
Ejemplo 4-25: Etil-éster del ácido 2-((R)-1-bifenil-4-il-metil-2-etoxi-carbonil-etil-amino)-oxazol-4-carboxílico



A una suspensión del etil-éster del ácido (R)-4-bifenil-4-il-3-ureido-butírico (169 miligramos, 0.518 milimoles) en EtOH (5 mililitros) en un baño de hielo, se le agrega bromo-piruvato de etilo (0.098 mililitros, 0.777 milimoles). La reacción se calienta lentamente a temperatura ambiente, y se agita a reflujo durante la noche. La reacción se concentra, y el residuo se absorbe en EtOAc y H_2O. La capa orgánica combinada se lava con salmuera, y se seca sobre

sulfato de sodio anhidro, se filtra, y se concentra bajo presión reducida, para dar el etil-éster del ácido 2-((R)-1-bifenil-4-il-metil-2-etoxi-carbonil-etil-amino)-oxazol-4-carboxílico. HPLC - tiempo de retención = 1.42 minutos (condición B); MS (m+1) = 423.

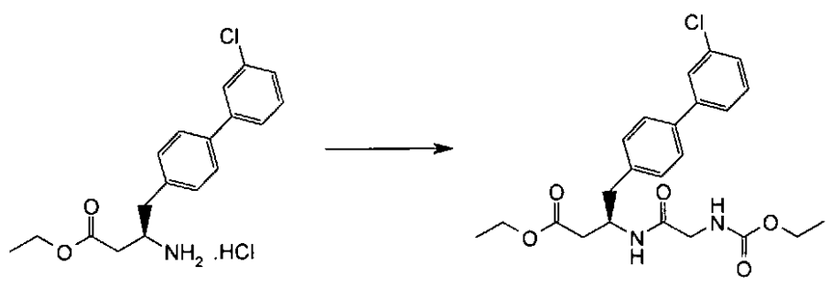
Ejemplo 4-26: Síntesis de 4-(4-(benciloxi)-1-(3'-cloro-bifenil-4-il)-4-oxo-butan-2-il-amino)-4-oxo-but-2-enoato de (R,E)-etilo



Al 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo (87.6 miligramos, 0.183 milimoles), se le agrega una solución de HCl en 1,4-dioxano (0.456 mililitros, 1.825 milimoles) a temperatura ambiente. Después de agitar durante 3 horas, la mezcla de reacción se concentra bajo presión reducida, para dar el clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo. Una mezcla de clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo, monoetil-éster del ácido fumárico (33.4 miligramos, 0.220 milimoles), EDCI (63.3 miligramos, 0.330 milimoles), di-isopropil-etil-amina (0.058 mililitros, 0.330 milimoles), y HOAt (44.9 miligramos, 0.330 milimoles) en N,N-dimetil-formamida (1.8 mililitros) se deja agitándose a temperatura ambiente durante 3 horas. La mezcla de reacción se diluye con agua, y entonces los productos se extraen con

EtOAc. La capa orgánica se lava con NH_4OH, HCl 1M acuoso, y salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra, para dar el producto crudo. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea en gel de sílice (heptano/EtOAc = 100:0 a 0:100), para dar 4-(4-(benciloxi)-1-(3'-cloro-bifenil-4-il)-4-oxo-butan-2-il-amino)-4-oxo-but-2-enoato de (R,E)-etilo (72.9 miligramos); HPLC - tiempo de retención = 1.40 minutos (condición B); MS (m+1) = 506.3; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.31 (t, *J* = 7.1 Hz, 3 H) 2.58 (A de ABX, J_{ab} = 16.4 Hz, J_{ax} = 5.3 Hz, 1 H) 2.6 (B de ABX, J_{ab} = 16.4 Hz, J_{bx} = 5.1 Hz, 1 H) 2.88 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.1 Hz, 1 H) 3.03 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.3 Hz, 1 H) 4.24 (q, *J* = 7.1 Hz, 2 H) 4.56 – 4.64 (m, 1 H) 5.12 (A de AB, *J* = 12.1 Hz, 1 H) 5.18 (B de AB, *J* = 12.1 Hz, 1 H) 6.57 (br d, *J* = 9.1 Hz, 1 H) 6.77 (A de AB, *J* = 15.4 Hz, 1 H) 6.81 (B de AB, *J* = 15.4 Hz, 1 H) 7.19 (br d, *J* = 8.1 Hz, 2 H) 7.29 – 7.47 (m, 10 H) 7.53 – 7.54 (m, 1 H).

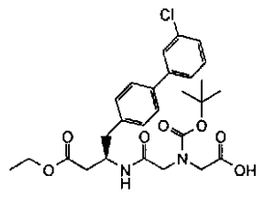
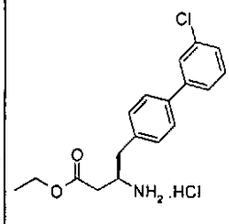
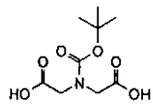
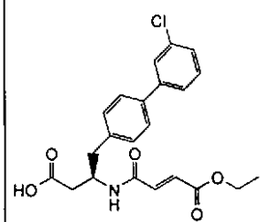
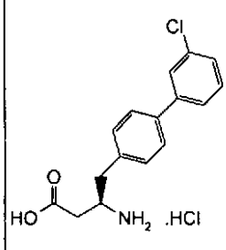
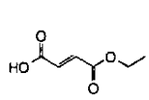
Ejemplo 4-27: Síntesis de 4-(3'-cloro-bifenil-4-il)-3-(2-(etoxi-carbonil-amino)acetamido)-butanoato de (R)-etilo



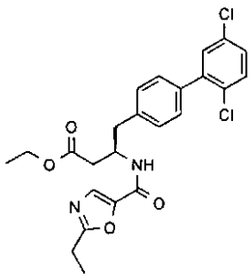
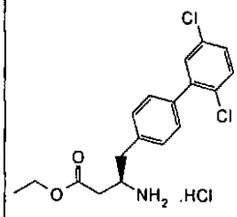
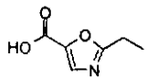
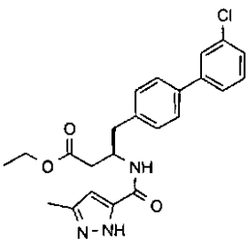
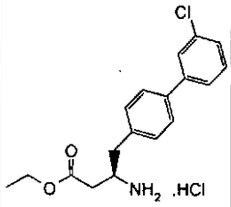
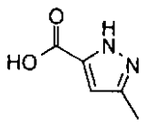
Una mezcla de clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-

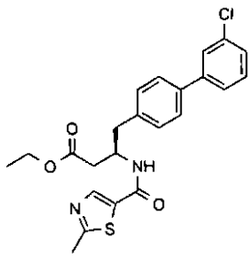
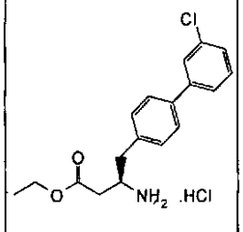
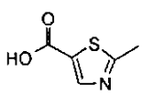
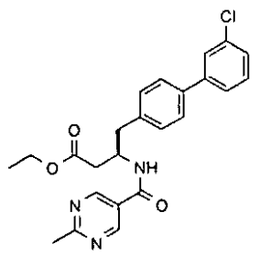
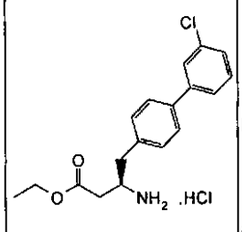
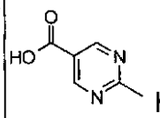
butanoato de (R)-etilo (173 miligramos, 0.488 milimoles), ácido 2-(etoxi-carbonil-amino)-acético (86 miligramos, 0.488 milimoles), EDCI (140 miligramos, 0.732 milimoles), di-isopropil-etil-amina (0.128 mililitros, 0.732 milimoles), y HOAt (100 miligramos, 0.732 milimoles) en N,N-dimetil-formamida (2.5 mililitros) se deja agitándose a temperatura ambiente durante 1 hora. La mezcla de reacción se diluye con agua, y entonces el sólido precipitado se recolecta en un embudo, se lava con H_2O, y se seca bajo presión reducida, para dar el producto crudo. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea en gel de sílice (heptano/EtOAc = 100:0 a 0:100), para dar el 4-(3'-cloro-bifenil-4-il)-3-(2-(etoxi-carbonil-amino)acetamido)-butanoato de (R)-etilo (161 miligramos); HPLC - tiempo de retención = 1.16 minutos (condición B); MS (m+1) = 447.3; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.25 (t, *J* = 7.07 Hz, 3 H) 1.29 (t, *J* = 7.07 Hz, 3 H) 2.50 (A de ABX, J_{ab} = 16.2 Hz, J_{ax} = 5.3 Hz, 1 H) 2.54 (B de ABX, J_{ab} = 16.2 Hz, J_{bx} = 5.3 Hz, 1 H) 2.89 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.8 Hz, 1 H) 2.99 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.6 Hz, 1 H) 3.80 (be d, *J* = 5.8 Hz, 2 H) 4.12 – 4.23 (m, 4 H) 4.48 – 4.56 (m, 1 H) 5.15 (br s, 1 H) 6.64 (br d, *J* = 8.8 Hz, 1 H) 7.25 – 7 .27 (m, 2 H) 7.29 – 7.38 (m, 2 H) 7.43 – 7.46 (m, 1 H) 7.49 – 7.52 (m, 2 H) 7.55 – 7.56 (m, 1 H).

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 4-27:

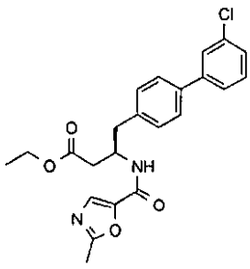
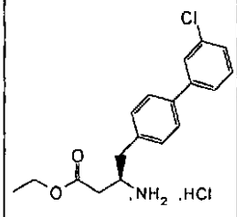
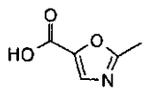
Ejemplo #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
Ejemplo 4-28	 ácido (R)-2-(terbutoxi-carbonil-(2-(1-(3'-cloro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-2-oxo-etil)-amino)-acético		 EDCI, HOAT, DIPEA, N,N-dimetil-formamida, rt	1.53 minutos. (A)	533.2
Ejemplo 4-29	 ácido (*R,E*)-4-(3'-cloro-bifenil-4-il)-3-(4-etoxi-4-oxo-but-2-enamido)-butanoico		 EDCI, HOAT, DIPEA, N,N-dimetil-formamida,	1.00 minutos. (B)	416.1

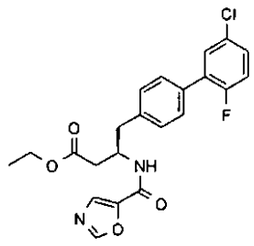
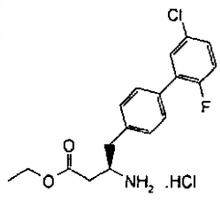
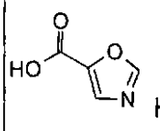
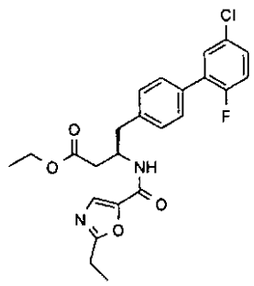
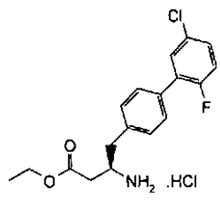
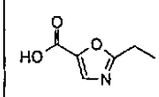
252

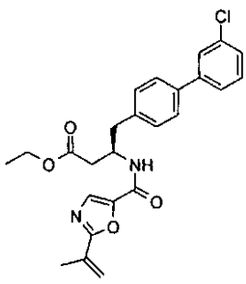
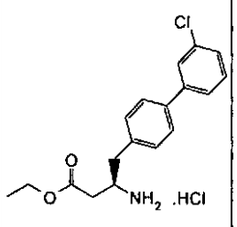
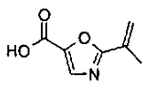
Ejemplo #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
			rt		
Ejemplo 4-30	 etil-éster del ácido (R)-4-(2',5'-dicloro-bifenil-4-il)-3-[(2-etil-oxazol-5-carbonil)-amino]-butírico		 HATU, trietil-amina, N,N-dimetil-formamida/ DCM, rt	1.64 minutos. (A)	476.2
Ejemplo 4-31	 etil-éster del ácido (R)-4-(3'-cloro-bifenil-4-il)-		 HATU, trietil-amina,	1.66 minutos. (A)	426.1

Ejemplo #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
	3-[(5-metil-2H-pirazol-3-carbonil)-amino]-butírico		N,N-dimetil-formamida/ DCM, rt		
Ejemplo 4-32	 etil-éster del ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(2-metil-tiazol-5-carbonil)-amino]-butírico		 HATU, trietil-amina, N,N-dimetil-formamida/ DCM, rt	1.69 minutos. (A)	443.2
Ejemplo 4-33	 etil-éster del		 ATU, trietil-amina,	1.66 minutos. (A)	438.2

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Ejemplo #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
	ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(2-metil-pirimidin-5-carbonil)-amino]-butírico		N,N-dimetil-formamida/ DCM, rt		
Ejemplo 4-34	 etil-éster del ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(2-metil-oxazol-5-carbonil)-amino]-butírico		 HATU, trietil-amina, N,N-dimetil-formamida/ DCM, rt	1.71 minutos. (A)	427.1

Ejemplo #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
Ejemplo 4-35	 etil-éster del ácido (R)-4-(5'-cloro-2'-fluoro-bifenil-4-il)-3-[(oxazol-5-carbonil)-amino]-butírico		 ATU, trietil-amina, N,N-dimetil-formamida/ DCM, rt	1.75 minutos. (A)	431.1
Ejemplo 4-36	 etil-éster del ácido (R)-4-(5'-cloro-2'-fluoro-		 HATU, trietil-amina, N,N-	1.81 minutos. (A)	459.1

Ejemplo #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
	bifenil-4-il)-3-[(2-etil-oxazol-5-carbonil)-amino]-butírico		dimetil-formamida/ DCM, rt		
Ejemplo 4-37	 4-(3'-cloro-bifenil-4-il)-3-(2-(prop-1-en-2-il)-oxazol-5-carboxamido)-butanoato de (R)-etilo		 HATU, trietil-amina, N,N-dimetil-formamida/ DCM, rt	1.86 minutos. (A)	453.2

Ejemplo 4-29: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.31 (t, J = 7.2 Hz, 3 H) 2.64 (A de ABX, J_{ab} = 16.8 Hz, J_{ax} = 5.1 HZ, 1 H) 2.68 (B de ABX, J_{ab} = 16.8 Hz, J_{bx} = 5.1 Hz, 1 H) 2.97 (A de ABX, J_{ab} = 13.7 Hz, J_{ax} = 8.1 HZ, 1 H) 3.08 (B de ABX, J_{ab} = 13.7 Hz, J_{bx} = 6.7

Hz, 1 H) 4.25 (q, *J* = 7.2 Hz, 2 H) 4.58 – 4.67 (m, 1 H) 6.66 (d, J = 8.8 Hz, 1 H) 6.80 (A de AB, J = 15.4 Hz, 1 H) 6.97 (B de AB, J = 15.4 Hz, 1 H) 7.27 – 7.37 (m, 4 H) 7.43 – 7.45 (m, 1 H) 7.51 (d, *J* = 8.3 Hz, 2 H) 7.55 – 7.56 (m, 1 H).

Ejemplo 4-30: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.21 (t, J=7.2 Hz, 3 H) 1.34 (t, J=7.6 Hz, 3 H) 2.68 (d, J=6.8 Hz, 2 H) 2.84 - 2.87 (m, 2 H) 2.98 - 3.00 (m, 2 H) 4.10 (q, J=7.1 Hz, 2 H) 4.66 - 4.78 (m, 1 H) 7.27 - 7.37 (m, 6 H) 7.41 - 7.47 (m, 1 H) 7.54 (s, 1 H).

Ejemplo 4-31: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.20 (t, J=7.1 Hz, 3 H) 2.28 (s, 3 H) 2.62 (d, J=7.1 Hz, 2 H) 2.93 (dd, J=13.6, 6.8 Hz, 1 H) 3.00 (dd, J=13.6, 7.3 Hz, 1 H) 4.09 (q, J=7.1 Hz, 2 H) 4.60 - 4.76 (m, 1 H) 6.45 (s, 1 H) 7.24 - 7.40 (m, 4 H) 7.42 - 7.51 (m, 3 H) 7.54 (t, J=1.8 Hz, 1 H).

Ejemplo 4-32: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.20 (t, J=7.2 Hz, 3 H) 2.58 - 2.66 (m, 2 H) 2.68 (s, 3 H) 2.94 (dd, J=14.2, 7.8 Hz, 1 H) 2.99 (dd, J=13.6, 6.8 Hz, 1 H) 4.09 (q, J=7.2 Hz, 2 H) 4.58 - 4.76 (m, 1 H) 7.27 - 7.31 (m, 1 H) 7.33 (d, J=8.3 Hz, 2 H) 7.37 (t, J=7.8 Hz, 1 H) 7.46 - 7.49 (m, 1 H) 7.51 (d, J=8.1 Hz, 2 H) 7.55 (t, J=1.9 Hz, 1 H) 8.06 (s, 1 H) 8.49 (d, J=8.6 Hz, 1 H).

Ejemplo 4-33: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.21 (t, J=7.1 Hz, 3 H) 2.60 - 2.70 (m, 2 H) 2.72 (s, 3 H) 2.97 (dd, J=13.6, 8.1 Hz, 1 H) 3.03 (dd, J=13.9, 6.6 Hz, 1 H) 4.11 (q, J=7.2 Hz, 2 H) 4.67 - 4.81 (m, 1 H) 7.27 - 7.33 (m, 1 H) 7.33 - 7.41 (m, 3 H) 7.48 - 7.52 (m, 1 H) 7.54 (d, J=8.3 Hz, 2 H) 7.57 (t, J=1.8 Hz, 1 H) 8.70 (d, J=8.3 Hz, 1 H) 8.92 (s, 2 H).

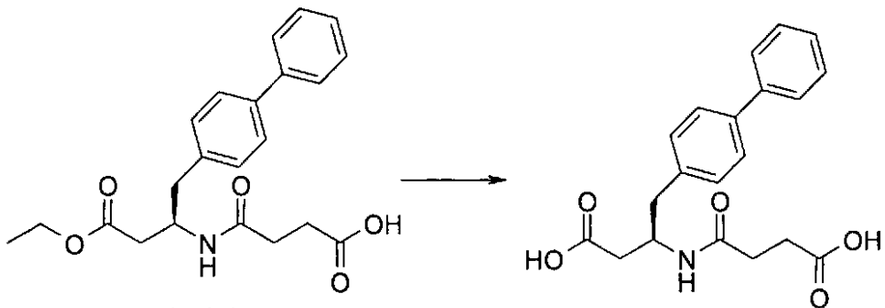
Ejemplo 4-34: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.21 (t, J=7.2 Hz, 3 H) 2.43 (s, 3 H) 2.63 (d, J=6.6 Hz, 2 H) 2.94 (dd, J=13.9, 7.1 Hz, 1 H) 2.99 (dd, J=13.6, 7.6 Hz, 1 H) 4.10 (q, J=7.1 Hz, 2 H) 4.62 - 4.74 (m, 1 H) 7.26 - 7.30 (m, 1 H) 7.30 - 7.39 (m, 3 H) 7.43 - 7.51 (m, 3 H) 7.53 (t, J=1.8 Hz, 1 H) 8.15 (s, 1 H).

Ejemplo 4-35: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.20 (t, J=7.1 Hz, 3 H) 2.64 (dd, J=15.4, 7.3 Hz, 1 H) 2.70 (dd, J=15.9, 6.3 Hz, 1 H) 2.99 (d, J=7.3 Hz, 2 H) 4.10 (q, J=7.2 Hz, 2 H) 4.65 - 4.79 (m, 1 H) 7.14 (dd, J=10.2, 8.7 Hz, 1 H) 7.30 (ddd, J=8.8, 4.1, 2.8 Hz, 1 H) 7.32 - 7.37 (m, 2 H) 7.37 - 7.46 (m, 3 H) 7.67 (s, 1 H) 8.28 (s, 1 H) 8.62 (d, J=8.6 Hz, 1 H).

Ejemplo 4-36: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.20 (t, J=7.2 Hz, 3 H) 1.33 (t, J=7.7 Hz, 3 H) 2.66 (d, J=6.8 Hz, 2 H) 2.83 (q, J=7.6 Hz, 2 H) 2.98 (d, J=7.1 Hz, 2 H) 4.10 (q, J=7.1 Hz, 2 H) 4.65 - 4.79 (m, 1 H) 7.14 (dd, J=10.2, 8.7 Hz, 1 H) 7.30 (ddd, J=8.8, 4.1, 2.8 Hz, 1 H) 7.32 - 7.37 (m, 2 H) 7.37 - 7.46 (m, 3 H) 7.54 (s, 1 H) 8.49 (d, J=8.8 Hz, 1 H).

Ejemplo 4-37: ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.33 (t, *J*=7.1 Hz, 3 H) 2.22 (s, 3 H) 2.57 - 2.72 (m, 2 H) 2.99 (dd, *J*=13.6, 8.1 Hz, 1 H) 3.16 (dd, *J*=13.6, 6.3 Hz, 1 H) 4.15 - 4.33 (m, 2 H) 4.60 - 4.82 (m, 1 H) 5.55 (s, 1 H) 6.10 (s, 1 H) 7.15 (d, *J*=8.8 Hz, 1 H) 7.34 (d, *J*=8.1 Hz, 3 H) 7.39 (t, *J*=7.7 Hz, 1 H) 7.48 (dt, *J*=7.6, 1.5 Hz, 1 H) 7.54 (d, *J*=8.1 Hz, 2 H) 7.58 (t, *J*=1.8 Hz, 1 H) 7.72 (s, 1 H).

Ejemplo 5-1: Síntesis de ácido (R)-4-(bifenil-4-il)-3-(3-carboxi-propanamido)-butanoico

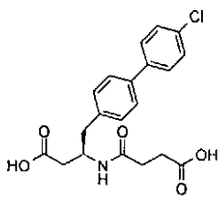
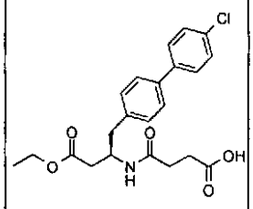
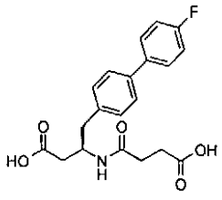
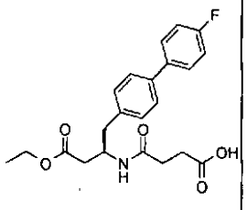


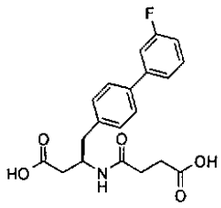
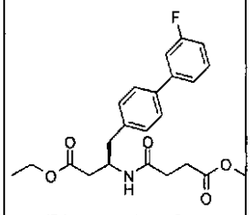
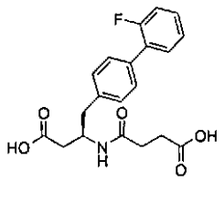
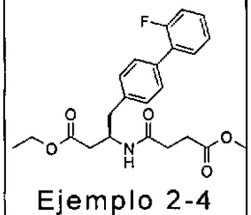
Ejemplo 1-1

A una solución del ácido (R)-4-(1-(bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico (61.2 miligramos, 0.160 milimoles) en tetrahidrofurano (1.6 mililitros), y metanol (0.2 mililitros), se le agrega una solución acuosa de NaOH 1M (0.638 mililitros, 0.638 milimoles) a temperatura ambiente. Después de agitar durante 45 minutos, la reacción se apaga con HCl acuoso 0.1 M, y se extrae con acetato de etilo. La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida, para dar el ácido (R)-4-(bifenil-4-il)-3-(3-carboxi-propanamido)-butanoico (54.9 miligramos). HPLC - tiempo de retención = 1.33 minutos (condición A); MS (m+1) = 356.1; ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.40-2.56 (m, 6 H) 2.83 - 2.94 (m, 2 H) 4.43 - 4.50 (m, 1 H) 7.29-7.32 (m, 3 H) 7.41 (t, 2 H, J = 7.7 Hz) 7.53-7.60 (m, 4H).

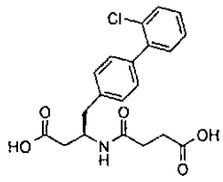
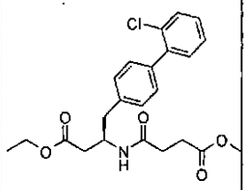
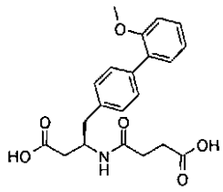
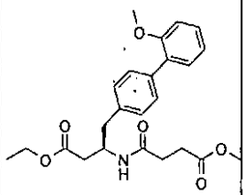
Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 5-1:

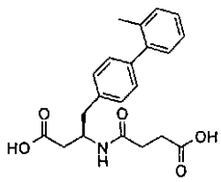
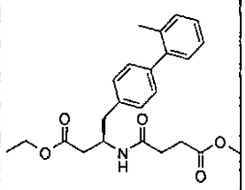
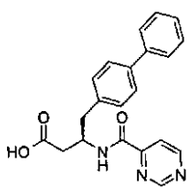
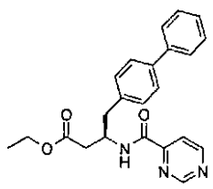
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Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 5-2	 ácido (R)-3-(3-carboxi-propionil-amino)-4-(4'-cloro-bifenil-4-il)-butírico	 Ejemplo 2-2	NaOH acuoso, tetra-hidro-furano, MeOH, rt	1.10 minutos. (A)	389.9
Ejemplo 5-3	 ácido (R)-3-(3-carboxi-propionil-amino)-4-(4'-fluoro-bifenil-4-il)-butírico	 Ejemplo 2-1	NaOH acuoso, tetra-hidro-furano, MeOH, rt	0.87 minutos. (A)	373.9

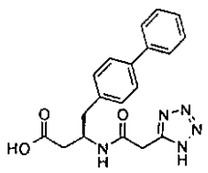
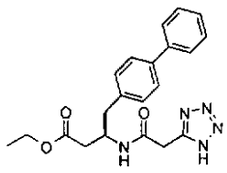
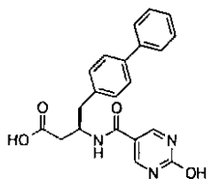
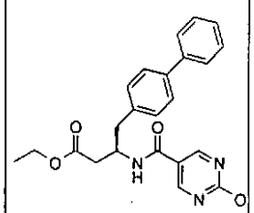
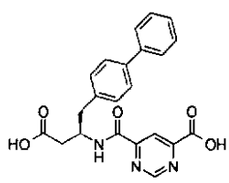
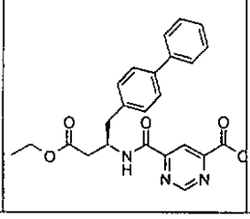
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 5-4	 ácido (R)-3-(3-carboxi-propionil-amino)-4-(3'-fluoro-bifenil-4-il)-butírico	 Ejemplo 2-3	NaOH acuoso, tetra-hidro-furano, MeOH, rt	0.69 minutos. (B)	374.0
Ejemplo 5-5	 ácido (R)-3-(3-carboxi-propionil-amino)-4-(2'-fluoro-bifenil-4-il)-butírico	 Ejemplo 2-4	NaOH acuoso, tetra-hidro-furano, MeOH, rt	0.80 minutos. (B)	373.9

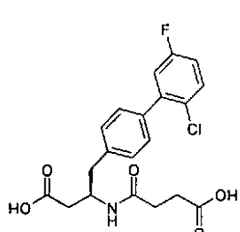
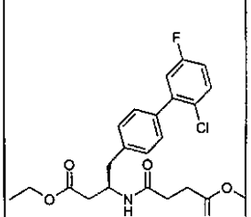
857

Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 5-6	 ácido (R)-3-(3-carboxi-propionil-amino)-4-(2'-cloro-bifenil-4-il)-butírico	 Ejemplo 2-5	NaOH acuoso, tetra-hidro-furano, MeOH, rt	0.74 minutos. (B)	390.0
Ejemplo 5-7	 ácido (R)-3-(3-carboxi-propionil-amino)-4-(2'-metoxi-bifenil-4-il)-butírico	 Ejemplo 2-6	NaOH acuoso, tetra-hidro-furano, MeOH, rt	0.61 minutos. (B)	386.1

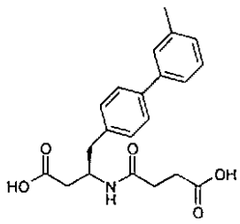
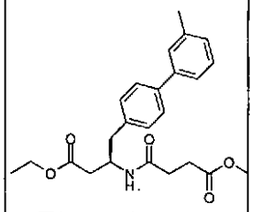
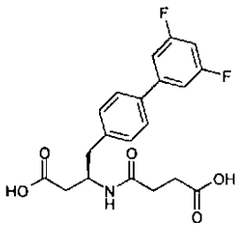
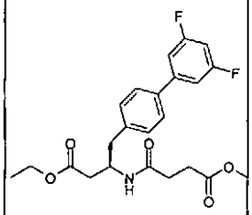
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 5-8	 ácido (R)-3-(3-carboxi-propionil-amino)-4-(2'-metil-bifenil-4-il)-butírico	 Ejemplo 2-7	NaOH acuoso, tetra-hidro-furano, MeOH, rt	0.94 minutos. (B)	370.0
Ejemplo 5-9	 ácido (R)-4-bifenil-4-il-3-[(pirimidin-4-carbonil)-amino]-butírico	 Ejemplo 3-3	LiOH acuoso, EtOH, rt.	0.67 minutos. (B)	362.0

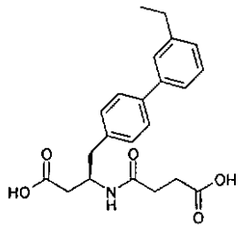
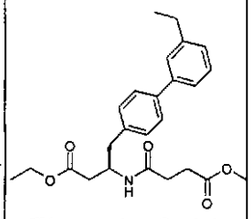
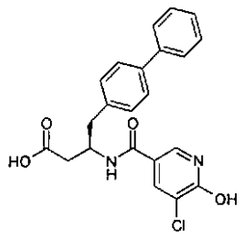
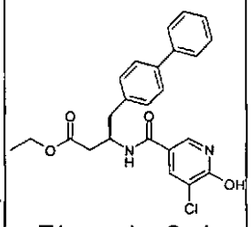
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Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 5-10	 ácido (R)-4-bifenil-4-il-3-(2-1H-tetrazol-5-il-acetil-amino)-butírico	 Ejemplo 4-1	NaOH acuoso, MeOH, RT	1.19 minutos. (C)	366.0
Ejemplo 5-11	 ácido (R)-4-bifenil-4-il-3-[(2-hidroxi-pirimidin-5-carbonil)-amino]-butírico	 Ejemplo 3-2	NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.28 minutos. (A)	377.9
Ejemplo 5-12			NaOH acuoso, tetra-	0.80 minutos. (B)	406.0

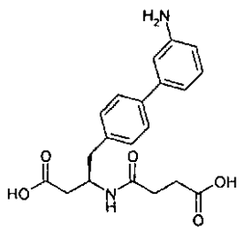
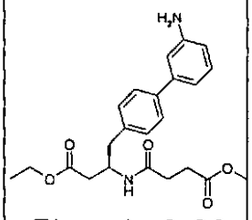
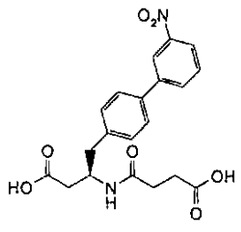
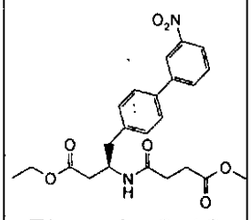
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
	ácido 6-((R)-1-bifenil-4-il-metil-2-carboxi-etil-carbamoil)-pirimidin-4-carboxílico	Ejemplo 3-1	hidro-furano, MeOH, RT		
Ejemplo 5-13	 ácido (R)-4-(1-carboxi-3-(2'-cloro-5'-fluoro-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico	 Ejemplo 2-8	NaOH acuoso, tetra-hidro-furano, MeOH, RT	0.74 minutos. (B)	408.2

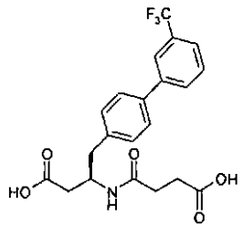
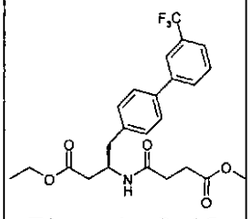
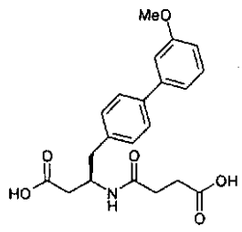
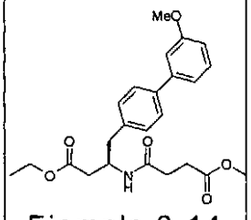
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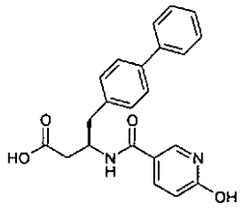
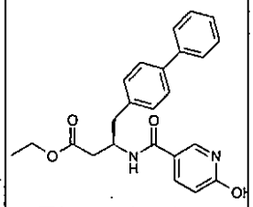
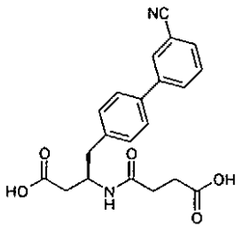
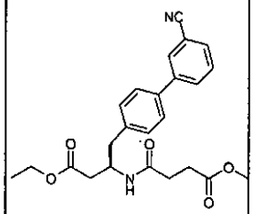
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 5-14	 ácido (R)-4-(1-carboxi-3-(3'-metil-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico	 Ejemplo 2-9	NaOH acuoso, tetra-hidro-furano, MeOH, RT	0.55 minutos. (B)	370.1
Ejemplo 5-15	 ácido (R)-4-(1-carboxi-3-(3',5'-difluoro-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico	 Ejemplo 2-10	NaOH acuoso, tetra-hidro-furano, MeOH, RT	0.46 minutos. (B)	392.1

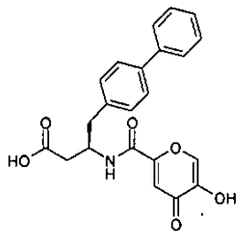
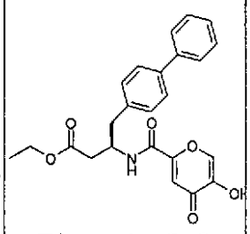
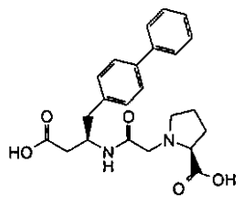
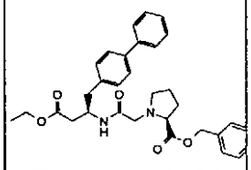
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 5-16	 ácido (R)-4-(1-carboxi-3-(3'-etil-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico	 Ejemplo 2-11	NaOH acuoso, tetra-hidro-furano, MeOH, RT	0.70 minutos. (B)	384.3
Ejemplo 5-17	 ácido (R)-4-(bifenil-4-il)-3-(5-cloro-6-hidroxi-nicotinamido)-butanoico	 Ejemplo 3-4	NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.40 minutos. (A)	411.2

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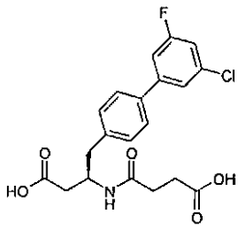
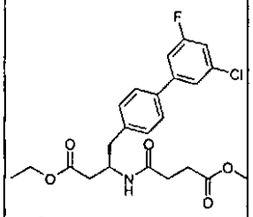
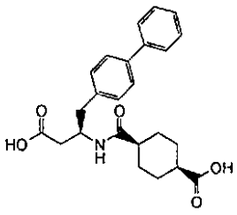
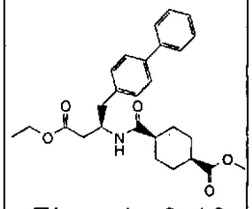
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 5-18	 ácido (R)-4-(3'-amino-bifenil-4-il)-3-(3-carboxi-propanamido)-butanoico	 Ejemplo 3-20	NaOH acuoso, tetra-hidro-furano, MeOH, RT	0.88 minutos. (A)	371.2
Ejemplo 5-19	 ácido (R)-4-(1-carboxi-3-(3'-nitro-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico	 Ejemplo 2-12	NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.41 minutos. (D)	401.2

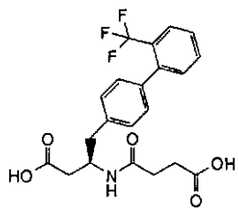
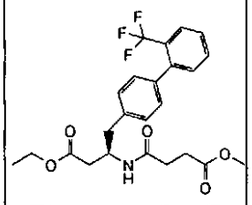
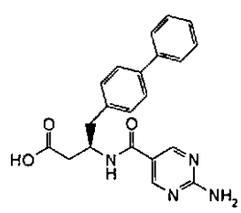
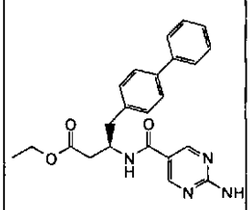
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 5-20	 ácido (R)-4-(1-carboxi-3-(3'-(trifluoro-metil)-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico	 Ejemplo 2-13	NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.59 minutos. (H)	424.2
Ejemplo 5-21	 ácido (R)-4-(1-carboxi-3-(3'-metoxi-bifenil-4-il)-propan-2-il-amino)-4-oxo-	 Ejemplo 2-14	NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.44 minutos. (H)	386.2

Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
	butanoico				
Ejemplo 5-22	 ácido (R)-4-(bifenil-4-il)-3-(6-hidroxi-nicotinamido)-butanoico	 Ejemplo 3-5	NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.29 minutos. (B)	377.1
Ejemplo 5-23	 ácido (R)-4-(1-carboxi-3-(3'-cianobifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico	 Ejemplo 2-15	NaOH acuoso, tetra-hidro-furano, MeOH, RT	0.49 minutos. (B)	381.1

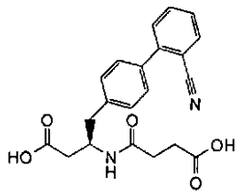
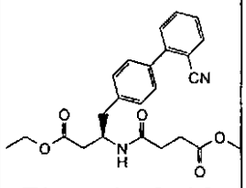
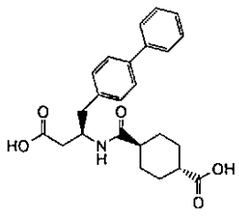
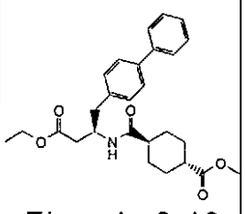
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 5-24	 ácido (R)-4-(bifenil-4-il)-3-(5-hidroxi-4-oxo-4H-piran-2-carboxamido)-butanoico	 Ejemplo 3-6	NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.36 minutos. (A)	394.0
Ejemplo 5-26	 sal de ácido trifluoro-acético del ácido (S)-1-(2-((R)-1-(bifenil-4-il)-3-carboxi-propan-2-il-	 Ejemplo 3-23	NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.20 minutos. (A)	411.2

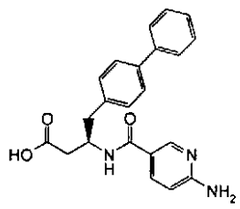
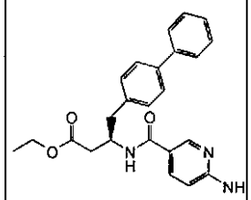
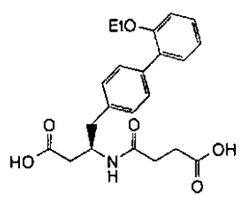
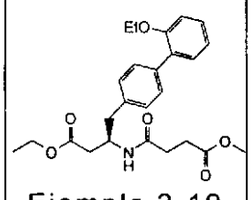
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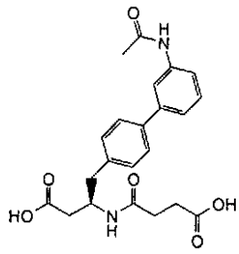
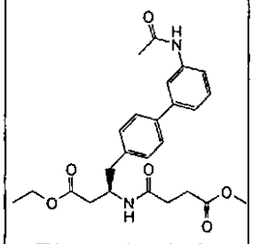
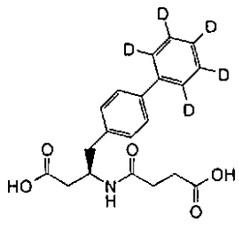
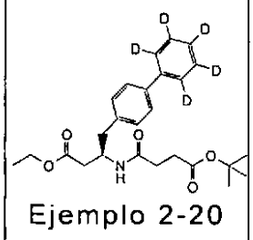
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
	amino)-2-oxo-etil)-pirrolidin-2-carboxílico				
Ejemplo 5-27	 ácido (R)-4-(1-carboxi-3-(3'-cloro-5'-fluoro-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico	 Ejemplo 2-16	NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.02 minutos. (B)	408.1
Ejemplo 5-28	 ácido (1S,4s)-4-((R)-1-(bifenil-4-	 Ejemplo 3-12	NaOH acuoso, tetra-hidro-furano, MeOH,	0.82 minutos. (B)	410.1

Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
	il)-3-carboxi-propan-2-il-carbamoil)-ciclohexan-carboxílico		RT		
Ejemplo 5-29	 ácido (R)-4-(1-carboxi-3-(2'-(trifluoro-metil)-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico	 Ejemplo 2-17	NaOH acuoso, tetra-hidro-furano, MeOH, RT	0.53 minutos. (B)	424.0
Ejemplo 5-30		 Ejemplo 3-7	NaOH acuoso, tetra-hidro-	1.36 minutos. (A)	377.0

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Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
	ácido (R)-3-(2-amino-pirimidin-5-carboxamido)-4-(bifenil-4-il)-butanoico		furano, MeOH, RT		
Ejemplo 5-31	 ácido (R)-4-(1-carboxi-3-(2'-cianobifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico	 Ejemplo 2-18	NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.11 minutos. (A)	381.1
Ejemplo 5-32	 ácido (1R,4r)-4-	 Ejemplo 3-13	NaOH acuoso, tetra-hidro-furano,	0.61 minutos. (B)	410.1

Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
	((R)-1-(bifenil-4-il)-3-carboxi-propan-2-il-carbamoil)-ciclohexan-carboxílico		MeOH, RT		
Ejemplo 5-33	 ácido (R)-3-(6-amino-nicotinamido)-4-(bifenil-4-il)-butanoico	 Ejemplo 3-8	NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.28 minutos. (A)	376.2
Ejemplo 5-34	 ácido (R)-4-(1-	 Ejemplo 2-19	NaOH acuoso, tetra-hidro-furano,	1.51 minutos. (D)	400.5

Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
	carboxi-3-(2'-etoxi-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico		MeOH, RT		
Ejemplo 5-35	 ácido (R)-4-(3'-acetamido-bifenil-4-il)-3-(3-carboxi-propanamido)-butanoico	 Ejemplo 3-24	NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.18 minutos. (D)	413.2
Ejemplo 5-36		 Ejemplo 2-20	NaOH acuoso, tetra-hidro-	0.68 minutos. (B)	361.2

Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	HPLC-RT (condición)	MS (M+1)
	ácido (R)-4-(1-carboxi-3-(2',3',4',5',6'-d5-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico		furano, MeOH, 50°C		

Ejemplo 5-2: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.38-2.42 (m, 2 H) 2.45 - 2.54 (m, 4 H) 2.82- 2.94 (m, 2 H) 4.42 - 4.48 (m, 1 H) 7.12 - 7.16 (m, 2 H) 7.31 (d, J=8.4 Hz, 2 H) 7.41 (d, J = 8.6 Hz, 2 H) 7.54 (d, J = 8.1 Hz, 2 H) 7.58 (d, J = 8.6 Hz,2 H).

Ejemplo 5-3: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39-2.42 (m, 2 H) 2.45 - 2.54 (m, 4 H) 2.85 (A de ABX, Jab = 13.6 Hz, Jax = 7.6 HZ, 1 H) 2.91 (B de ABX, Jab = 13.6 Hz, Jbx = 6.2 HZ, 1 H) 4.42 - 4.48 (m, 1 H) 7.12 – 7.16 (m,2 H) 7.31 (A de AB, J = 8.2 Hz, 2 H) 7.52 (B de AB, J = 8.2 Hz, 2 H) 7.58 – 7.62 (m, 2 H)

Ejemplo 5-4: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39-2.44 (m, 2 H) 2.46 - 2.55 (m, 4 H) 2.86 (A de ABX, Jab = 13.6 Hz, Jax = 7.6 HZ, 1 H) 2.92 (B de ABX, Jab = 13.6 Hz, Jbx = 6.3 HZ, 1 H) 4.42 - 4.49

(m, 1 H) 7.01 – 7.06 (m,1 H) 7.32 (br d, J = 8.1 Hz, 2 H) 7.39 – 7.45 (m, 2 H) 7.55 (d, J = 8.1 Hz, 2 H)

Ejemplo 5-5: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.40-2.43 (m, 2 H) 2.46 - 2.56 (m, 4 H) 2.87 (A de ABX, Jab = 13.5 Hz, Jax = 7.7 HZ, 1 H) 2.93 (B de ABX, Jab = 13.5 Hz, Jbx = 6.2 HZ, 1 H) 4.43 - 4.50 (m, 1 H) 7.13 – 7.18 (m, 1 H) 7.20 – 7.24 (m, 1 H) 7.31– 7.35 (m,3 H) 7.44 – 7.48 (m, 3 H) 7.99 (br d, J = 8.3 Hz, 1 H)

Ejemplo 5-6: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39-2.43 (m, 2 H) 2.45 - 2.57 (m, 4 H) 2.87 (A de ABX, Jab = 13.6 Hz, Jax = 7.6 HZ, 1 H) 2.94 (B de ABX, Jab = 13.6 Hz, Jbx = 6.1 HZ, 1 H) 4.44 - 4.51 (m, 1 H) 7.28 – 7.35 (m, 7 H) 7.46 (br d, J = 7.9 Hz, 1 H)

Ejemplo 5-7: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.40-2.52 (m, 6 H) 2.83 – 2.92 (m, 2 H) 3.77 (s, 3 H) 4.44 – 4.47 (m, 1 H) 6.96 – 7.05 (m, 2 H) 7.23 – 7.30 (m, 4 H) 7.39 -7.41 (m, 2 H)

Ejemplo 5-8: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.21 (s, 3 H) 2.41-2.55 (m, 6 H) 2.82 – 2.94 (m, 2 H) 3.77 (s, 3 H) 4.45 – 4.48 (m, 1 H) 7.15 – 7.28 (m, 8 H)

Ejemplo 5-9: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.56 (dd, J=5.81, 15.92Hz, 1H), 2.66 (dd, J=7.07, 15.92Hz, 1H), 2.90 (dd, J=6.06, 13.64Hz, 1H), 3.00 (dd, J=8.08, 13.64Hz, 1H), 4.53-4.64 (m, 1H), 7.30 (d, J=8.34Hz, 2H), 7.33 (t, J=7.58, 1H), 7.56 (d, J=8.34Hz, 2H), 7.62 (d, J=7.07Hz, 2H), 7.95 (dd, J=1.26, 5.05Hz, 1H), 9.01-9.07 (m, 2H), 9.33 (d, J=1.52Hz, 1H), 12.28 (s, 1H).

Ejemplo 5-10: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.36 - 2.49 (m, 2 H), 2.75 - 2.86 (m, 2 H), 3.83 (s, 2 H), 4.19 - 4.31 (m, 1 H), 7.26 (d,

J=8.3 Hz, 2 H), 7.31 - 7.38 (m, 1 H), 7.45 (t, J=7.6 Hz, 2 H), 7.56 (d, J=8.3 Hz, 2 H), 7.61 - 7.67 (m, 2 H), 8.40 (d, J=8.1 Hz, 1 H), 12.26 (br. s., 1 H), 16.02 (br. s., 1 H).

Ejemplo 5-11: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.46 - 2.59 (m, 2 H), 2.86 - 2.88 (m, 2 H), 4.41 - 4.49 (m, 1 H), 7.29 - 7.36 (m, 3 H), 7.42 – 7.46 (m, 2 H), 7.58 – 7.65 (m, 4 H), 8.26 (d, J=8 Hz, 1 H), 8.64 (br s, 2 H) 12.24 (br. s., 1 H).

Ejemplo 5-12: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.54 - 2.70 (m, 2 H), 2.88 – 3.03 (m, 2 H), 4.56 - 4.65 (m, 1 H), 7.29 - 7.34(m, 3 H), 7.41 – 7.45 (m, 2 H), 7.55 – 7.63 (m, 4 H), 8.33 (s, 1 H), 9.15 (d, J = 9.1 Hz, 1 H), 9.49 (s, 1 H), 12.30 (br s, 1 H), 14.11 (br s, 1 H).

Ejemplo 5-13: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.38 - 2.57 (m, 6 H) 2.87 (A de ABX, Jab = 13.6 Hz, Jax = 7.6 Hz, 1 H) 2.95 (B de ABX, Jab = 13.6 Hz, Jbx = 6.1 Hz, 1 H) 4.44 - 4.51 (m, 1 H) 7.06 - 7.14 (m, 2 H) 7.31 - 7.37 (m, 5 H) 7.48 (dd, J = 8.8 y 5.1 Hz, 1 H).

Ejemplo 5-14: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39 (s, 3 H) 2.39 - 2.55 (m, 6 H) 2.85 (A de ABX, Jab = 13.5 Hz, Jax = 7.5 HZ, 1 H) 2.90 (B de ABX, Jab = 13.5 Hz, Jbx = 6.4 Hz, 1 H) 4.42 – 4.49 (m, 1 H) 7.13 (br d, J = 7.3 Hz, 1 H) 7.26 – 7.30 (m, 3 H) 7.36 - 7.40 (m, 2 H) 7.52 (d, J = 8.3 Hz, 2 H).

Ejemplo 5-15: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.38 - 2.55 (m, 6 H) 2.86 (A de ABX, Jab = 13.6 Hz, Jax = 7.8 HZ, 1 H) 2.93 (B de ABX, Jab = 13.6 Hz, Jbx = 6.1 HZ, 1 H) 4.42 – 4.49 (m, 1 H) 6.86 - 6.92 (m, 1 H) 7.19 - 7.25 (m, 2 H) 7.33 - 7.35 (m, 2 H) 7.55 - 7.58 (m, 2 H).

Ejemplo 5-16: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.27 (t, J = 7.6 Hz, 3 H) 2.39 - 2.55 (m, 6 H) 2.70 (q, J = 7.6 Hz, 2 H) 2.85 (A de ABX, Jab = 13.6 Hz, Jax = 7.5 HZ, 1 H) 2.90 (B de ABX, Jab = 13.6 Hz, Jbx = 6.4 HZ, 1 H) 4.42 – 4.49 (m, 1 H) 7.16 (br d, J= 7.6 Hz, 1 H) 7.28 - 7.33 (m, 3 H) 7.38 - 7.42 (m, 2 H) 7.52 - 7.54 (m, 2 H).

Ejemplo 5-17: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.47 - 2.50 (m, 2 H) 2.82 - 2.91 (m, 2 H) 4.40 - 4.49 (m, 1 H) 7.29 (d, J = 8.3 Hz, 2 H) 7.31 - 7.36 (m, 1 H) 7.42 - 7.46 (m, 2 H) 7.59 (d, J = 8.4 Hz, 2 H) 7.63 - 7.65 (m, 2 H) 7.95 (br d, J = 2.3 Hz, 1 H) 8.11 (br d, J = 2.3 Hz, 1 H) 8.25 - 8.27 (m, 1 H) 12.24 (br s, 1 H) 12.48 (br s, 1 H).

Ejemplo 5-18: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.38 - 2.55 (m, 6 H) 2.86 (A de ABX, Jab = 13.6 Hz, Jax = 7.8 Hz, 1 H) 2.92 (B de ABX, Jab = 13.6 Hz, Jbx = 6.3 Hz, 1 H) 4.43 – 4.50 (m, 1 H) 7.26 (br d, J = 7.3 Hz, 1 H) 7.35 (d, J = 8.1 Hz, 2 H) 7.51 – 7.58 (m, 4 H) 7.64 (br d, J = 7.8 Hz, 1 H).

Ejemplo 5-19: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39 - 2.42 (m, 2 H) 2.45 - 2.56 (m, 4 H) 2.88 (A de ABX, Jab = 13.6 Hz, Jax = 7.6 Hz, 1 H) 2.95 (B de ABX, Jab = 13.6 Hz, Jbx = 6.2 Hz, 1 H) 4.44 – 4.51 (m, 1 H) 6.86 - 6.89 (m, 1 H) 7.38 - 7.41 (m, 2 H) 7.63 - 7.70 (m, 3 H) 8.02 - 8.04 (m, 1 H) 8.18 - 8.21 (m, 1 H) 8.45 (br t, J = 1.9 Hz, 1 H).

Ejemplo 5-20: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39 - 2.56 (m, 6 H) 2.87 (A de ABX, Jab = 13.6 Hz, Jax = 7.6 Hz, 1 H) 2.93 (B de ABX, Jab = 13.6 Hz, Jbx = 6.3 Hz, 1 H) 4.43 – 4.50 (m, 1 H) 7.36 (d, J = 8.3 Hz, 2 H) 7.58 – 7.62 (m, 4 H) 7.85 - 7.87 (m, 2 H).

Ejemplo 5-21: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39 - 2.54 (m, 6

H) 2.85 (A de ABX, Jab = 13.6 Hz, Jax = 7.5 Hz, 1 H) 2.91 (B de ABX, Jab = 13.6 Hz, Jbx = 6.3 HZ, 1 H) 3.84 (s, 3 H) 4.42 – 4.49 (m, 1 H) 6.86 - 6.89 (m, 1 H) 7.11 - 7.17 (m, 2 H) 7.29 - 7.34 (m, 3 H) 7.52 - 7.54 (m, 2 H).

Ejemplo 5-22: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.43 - 2.46 (m, 2 H), 2.81 - 2.91 (m, 2 H) 4.40 - 4.49 (m, 1 H) 6.33 (d, J = 9.6 Hz, 1 H) 7.28 - 7.35 (m, 3 H) 7.42 - 7.46 (m, 2 H) 7.58 (d, J = 8.1 Hz, 2 H) 7.63 - 7.65 (m, 2 H) 7.81 (dd, J = 9.6, 2.8 Hz, 1 H) 7.93 (br s, 1 H) 8.14 (d, J = 8.3 Hz, 1 H) 11.92 (br s, 1 H) 12.19 (br s, 1 H).

Ejemplo 5-23: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39 - 2.42 (m, 2 H) 2.44 - 2.55 (m, 4 H) 2.86 (A de ABX, Jab = 13.6 Hz, Jax = 7.6 Hz, 1 H) 2.93 (B de ABX, Jab = 13.6 Hz, Jbx = 6.3 HZ, 1 H) 4.43 – 4.50 (m, 1 H) 7.36 (d, J = 8.3 Hz, 2 H) 7.58 - 7.63 (m, 3 H) 7.66 - 7.69 (m,1 H) 7.91 - 7.94 (m, 1 H) 7.97 (br t, J = 1.5 Hz, 1 H).

Ejemplo 5-24: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.50 - 2.61 (m, 2 H) 2.83 - 2.94 (m, 2 H) 4.43 - 4.52 (m, 1 H) 6.82 (s, 1 H) 7.28 - 7.35 (m, 3 H) 7.44 (t, J = 7.7 Hz, 2 H) 7.58 - 7.65 (m, 4 H) 8.12 (s, 1 H) 8.86 (d, J = 8.3 Hz, 1 H) 9.55 (s, 1 H) 12.25 (br s, 1 H).

Ejemplo 5-25: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1.66 - 2.47 (m, 10 H) 2.71 - 2.83 (m, 2 H) 3.31 - 3.46 (m, 3 H) 4.18 - 4.49 (m, 2 H) 7.26 - 7.28 (m, 2 H) 7.32 - 7.36 (m, 1 H) 7.43 - 7.47 (m,2 H) 7.57 - 7.66 (m, 4 H) 7.86 (d, J = 8.3 Hz, 1 H) 12.31 (br s, 2 H).

Ejemplo 5-26: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1.80 - 2.03 (m, 3 H) 2.27 - 2.31 (m, 1 H) 2.39 - 2.52 (m, 2 H) 2.75 - 2.81 (m, 1 H) 2.85 - 2.89 (m, 1 H) 2.95 - 3.03 (m, 1 H) 3.41 - 3.78 (m, 2 H) 3.90 -

3.99 (m, 1 H) 4.14 - 4.20 (m, 1 H) 4.28 - 4.35 (m, 1 H) 7.28 - 7.37 (m, 3 H) 7.44 - 7.48 (m, 2 H) 7.58 - 7.65 (m,2 H) 8.45 (br s,1 H) 12.34 (br s, 1 H).

Ejemplo 5-27: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.38 - 2.54 (m, 6 H) 2.86 (A de ABX, Jab = 13.6 Hz, Jax = 7.6 Hz, 1 H) 2.93 (B de ABX, Jab = 13.6 Hz, Jbx = 6.2 HZ, 1 H) 4.42 – 4.49 (m, 1 H) 7.13 - 7.17 (m, 1 H) 7.31 - 7.37 (m,3 H) 7.46 - 7.47 (m, 1 H) 7.54 - 7.57 (m, 2 H).

Ejemplo 5-28: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.49 - 1.71 (m, 6 H) 2.01 - 2.11 (m, 2 H) 2.14 - 2.21 (m, 1 H) 2.44 - 2.56 (m, 3 H) 2.83 (A de ABX, Jab = 13.6 Hz, Jax = 8.0 Hz, 1 H) 2.91 (B de ABX, Jab = 13.6 Hz, Jbx = 6.3 HZ, 1 H) 4.43 – 4.51 (m, 1 H) 7.28 - 7.32 (m, 3 H) 7.38 - 7.42 (m,2 H) 7.52 (d, J = 8.1 Hz, 2 H) 7.56 - 7.59 (m, 2 H) 7.71 (br d, J = 8.6 Hz, 1 H).

Ejemplo 5-29: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39 - 2.42 (m, 2 H) 2.45 - 2.56 (m, 4 H) 2.87 (A de ABX, Jab = 13.6 Hz, Jax = 7.8 Hz, 1 H) 2.94 (B de ABX, Jab = 13.6 Hz, Jbx = 6.1 Hz, 1 H) 4.44 – 4.51 (m, 1 H) 7.23 (A de AB, J = 8.0 Hz, 2 H) 7.28 (B de AB, J = 8.0 Hz, 2 H) 7.35 (d, J = 7.6 Hz, 1 H) 7.50 - 7.53 (m, 1 H) 7.60 - 7.63 (m, 1 H) 7.75 (d, J = 7.8 Hz, 1 H)

Ejemplo 5-30: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.45 - 2.56 (m, 2 H) 2.83 - 2.93 (m, 2 H) 4.43 - 4.52 (m, 1 H) 7.18 (s, 2 H) 7.29 - 7.35 (m, 3 H) 7.42 - 7.46 (m, 2 H) 7.58 - 7.65 (m, 4 H) 8.19 (d, J = 8.1 Hz, 1 H) 8.60 (s, 2 H) 12.21 (br s, 1 H).

Ejemplo 5-31: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39 - 2.43 (m, 2

H) 2.46 - 2.57 (m, 4 H) 2.90 (A de ABX, Jab = 13.6 Hz, Jax = 7.8 Hz, 1 H) 2.97 (B de ABX, Jab = 13.6 Hz, Jbx = 6.1 Hz, 1 H) 4.45 – 4.52 (m, 1 H) 7.37 - 7.39 (m, 2 H) 7.49 - 7.53 (m, 3 H) 7.57 - 7.59 (m,1 H) 7.70 - 7.74 (m, 1 H) 7.80 - 7.82 (m, 1 H).

Ejemplo 5-32: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.33 - 1.49 (m, 4 H) 1.68 - 1.72 (m, 1 H) 1.79 - 1.83 (m, 1 H) 1.96 - 2.01 (m, 2 H) 2.05 - 2.13 (m, 1 H) 2.17 - 2.25 (m, 1 H) 2.43 - 2.55 (m, 2 H) 2.80 - 2.95 (m, 2 H) 4.42 - 4.49 (m, 1 H) 7.28 - 7.32 (m, 3 H) 7.38 - 7.43 (m, 2 H) 7.52 - 7.59 (m, 4 H).

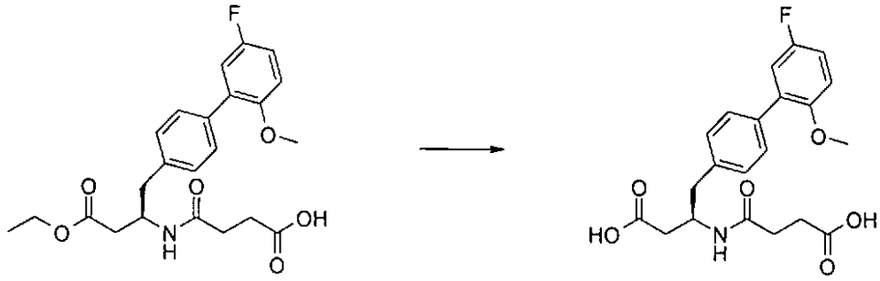
Ejemplo 5-33: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.48 - 2.55 (m, 2 H) 2.84 - 2.96 (m, 2 H) 4.44 - 4.53 (m, 1 H) 6.94 (br s, 1 H) 7.30 - 7.35 (m, 3 H) 7.42 - 7.46 (m, 2 H) 7.57 - 7.64 (m, 4 H) 8.17 - 8.60 (br m, 5 H) 12.27 (br s, 1 H).

Ejemplo 5-34: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.30 (t, J = 7.0 Hz, 3 H) 2.39 - 2.56 (m, 6 H) 2.82 - 2.93 (m, 2 H) 4.02 (q, J = 7.0 Hz, 2 H) 4.42 – 4.49 (m, 1 H) 6.96 - 7.03 (m, 2 H) 7.23 - 7.28 (m, 4 H) 7.44 (d, J = 8.4 Hz, 2 H).

Ejemplo 5-35: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.14 (s, 3 H) 2.39 - 2.43 (m, 2 H) 2.45- 2.56 (m, 4 H) 2.82 - 2.94 (m, 2 H) 4.02 (q, J = 7.0 Hz, 2 H) 4.42 – 4.49 (m, 1 H) 7.30 - 7.38 (m, 4 H) 7.49 - 7.55 (m, 3 H) 7.80 (br s, 1 H).

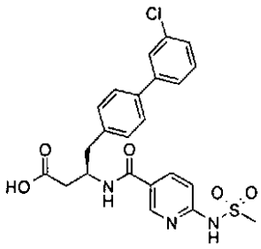
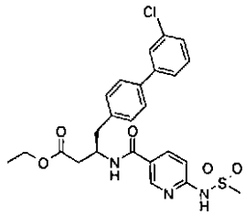
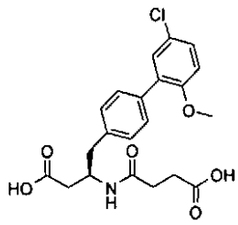
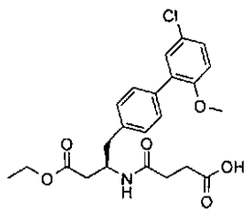
Ejemplo 5-36: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39 - 2.55 (m, 6 H) 2.85 (A de ABX, Jab = 13.6 Hz, Jax = 7.5 HZ, 1 H) 2.90 (B de ABX, Jab = 13.6 Hz, Jbx = 6.3 HZ, 1 H) 4.42 – 4.49 (m, 1 H) 6.86 - 6.92 (m, 1 H) 7.31 (d, J = 8.1 Hz, 2 H) 7.53 - 7.55 (m, 2 H).

Ejemplo 5-37: Síntesis de ácido (R)-4-(1-carboxi-3-(5'-fluoro-2'-metoxi-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico

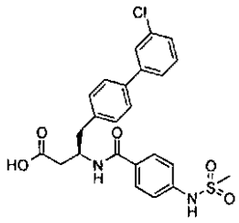
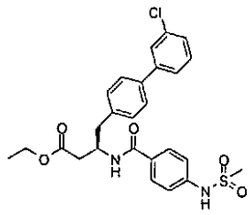
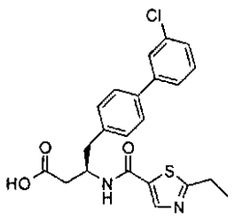
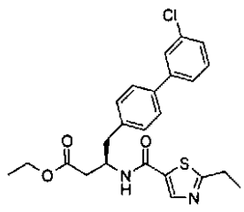


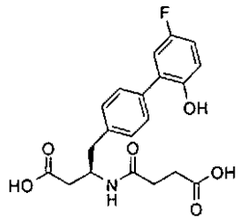
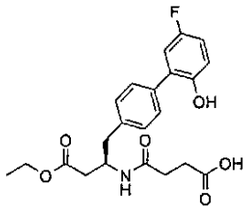
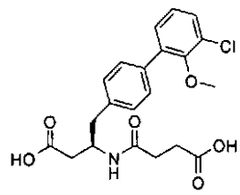
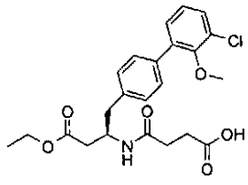
A una solución del ácido (R)-4-(4-etoxi-1-(5'-fluoro-2'-metoxi-bifenil-4-il)-4-oxo-butan-2-il-amino)-4-oxo-butanoico (83 miligramos, 0.192 milimoles) en metanol (2 mililitros), se le agrega NaOH 1N (4 mililitros, 4 milimoles) Después de agitar a temperatura ambiente durante 2 horas, el producto crudo se concentra bajo presión reducida para remover el metanol, y se diluye con EtOAc. La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante HPLC de fase inversa (SunFire C18, H_2O (ácido trifluoro-acético al 0.1 por ciento)/CH_3CN), y se liofiliza, para dar el ácido (R)-4-(1-carboxi-3-(5'-fluoro-2'-metoxi-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico (58 miligramos). HPLC - tiempo de retención = 1.46 minutos (condición D); MS (m+1) = 404.2; ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.36 - 2.59 (m, 6 H) 2.84 (dd, *J*=13.4, 6.3 Hz, 1 H) 2.91 (dd, *J*=13.4, 6.3 Hz, 1 H) 3.75 (s, 3 H) 4.34 - 4.56 (m, 1 H) 6.95 - 7.08 (m, 3 H) 7.26 (d, *J*=8.1 Hz, 2 H) 7.42 (d, *J*=8.3 Hz, 2 H)

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 5-37:

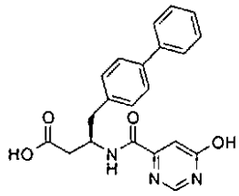
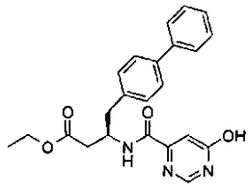
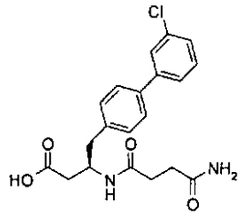
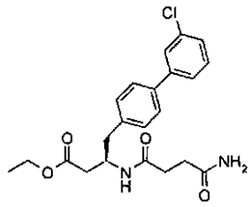
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
Ejemplo 5-38	 ácido R-4-(3'-cloro-bifenil-4-il)-3-(6-(metil-sulfonamido)-nicotinamido)-butanoico		NaOH acuoso, MeOH, rt	1.68 minutos. (D)	488.1
Ejemplo 5-39	 ácido R-4-(1-carboxi-3-(5'-cloro-2'-metoxi-bifenil-4-il)-propan-2-il-amino)-4-oxo-		NaOH acuoso, MeOH, rt	1.52 minutos. (D)	420.1

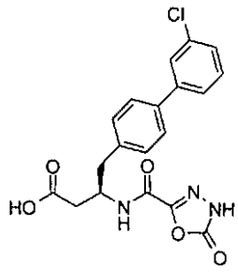
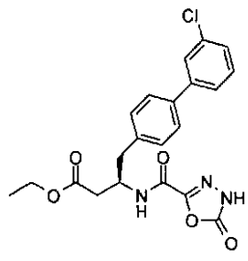
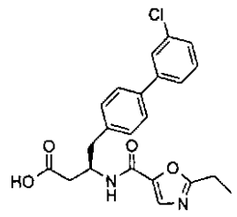
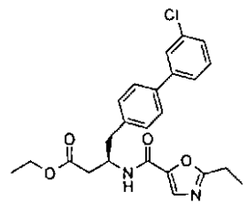
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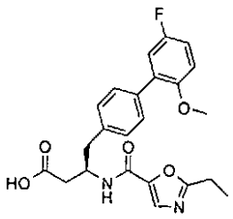
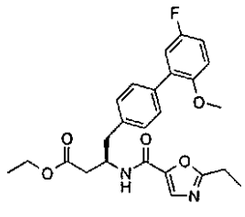
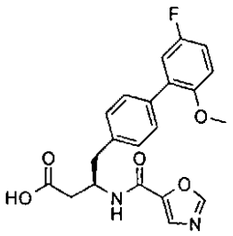
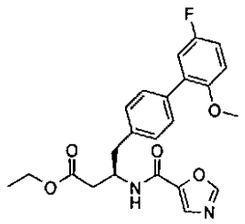
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
	butanoico				
Ejemplo 5-40	 ácido R-4-(3'-cloro-bifenil-4-il)-3-(4-(metil-sulfonamido)benzamido)-butanoico		NaOH acuoso, MeOH, rt	1.57 minutos. (D)	487.2
Ejemplo 5-41	 ácido R-4-(3'-cloro-bifenil-4-il)-3-(2-etil-tiazol-5-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.65 minutos. (D)	429.1

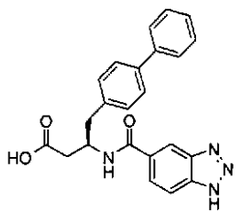
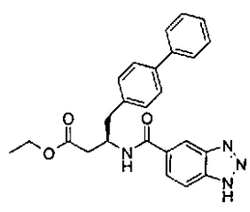
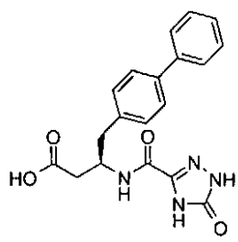
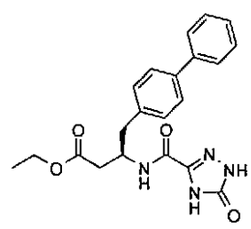
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
Ejemplo 5-42	 ácido R-4-(1-carboxi-3-(5'-fluoro-2'-hidroxi-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico		NaOH acuoso, MeOH, rt	1.42 minutos. (D)	390.2
Ejemplo 5-43	 ácido R-4-(1-carboxi-3-(3'-cloro-2'-metoxi-bifenil-4-il)-propan-2-il-amino)-4-oxo-		NaOH acuoso, MeOH, rt	1.53 minutos. (D)	420.2

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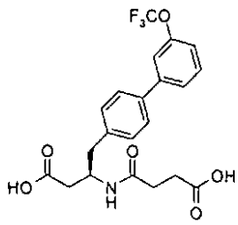
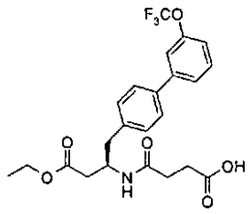
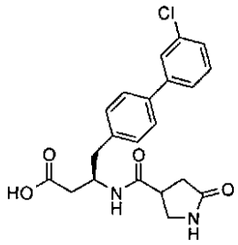
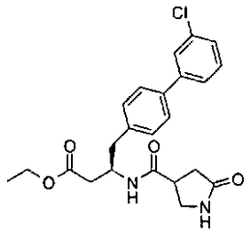
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
	butanoico				
Ejemplo 5-44	 ácido R-4-(bifenil-4-il)-3-(6-hidroxi-pirimidin-4-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.45 minutos. (D)	378.1
Ejemplo 5-45	 ácido (R)-3-(4-amino-4-oxo-butanamido)-4-(3'-cloro-bifenil-4-il)-butanoico		NaOH acuoso, MeOH, rt	1.26 minutos. (A)	389.3

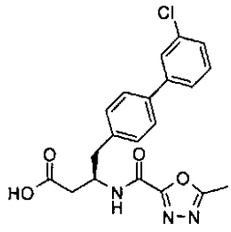
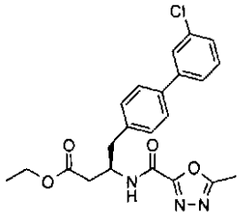
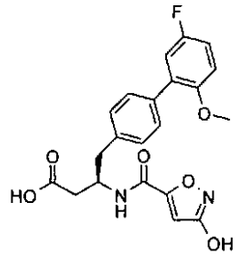
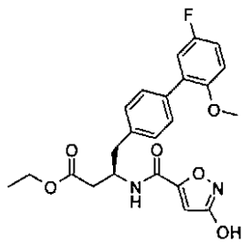
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
Ejemplo 5-46	 ácido R-4-(3'-cloro-bifenil-4-il)-3-(5-oxo-4,5-dihidro-1,3,4-oxadiazol-2-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.53 minutos. (D)	402.2
Ejemplo 5-47	 ácido R-4-(3'-cloro-bifenil-4-il)-3-(2-etil-oxazol-5-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.60 minutos. (D)	413.3

Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
Ejemplo 5-48	 ácido R-3-(2-etil-oxazol-5-carboxamido)-4-(5'-fluoro-2'-metoxi-bifenil-4-il)-butanoico		NaOH acuoso, MeOH, rt	1.38 minutos. (D)	427.2
Ejemplo 5-49	 ácido R-4-(5'-fluoro-2'-metoxi-bifenil-4-il)-3-(oxazol-5-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.37 minutos. (D)	399.3

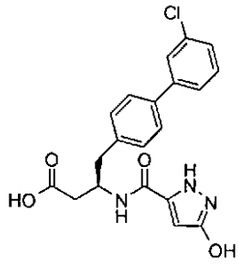
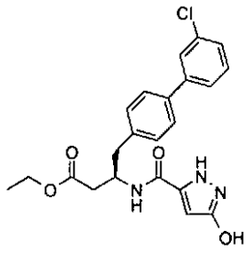
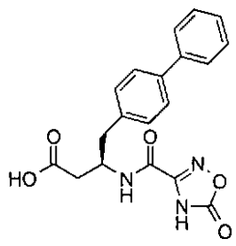
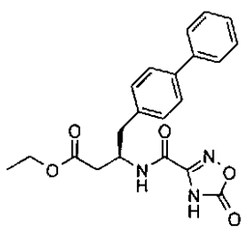
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
Ejemplo 5-50	 ácido R-3-(1H-benzo-[d][1,2,3]-triazol-5-carboxamido)-4-(bifenil-4-il)-butanoico		NaOH acuoso, MeOH, rt	1.50 minutos. (D)	401.1
Ejemplo 5-51	 ácido R-4-(bifenil-4-il)-3-(5-oxo-4,5-dihidro-1H-1,2,4-triazol-3-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.39 minutos. (D)	367.1

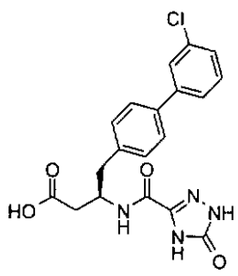
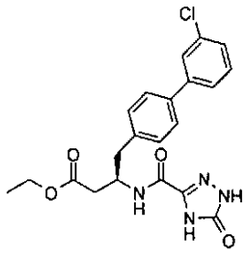
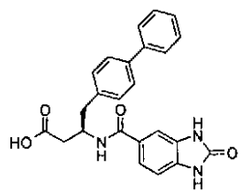
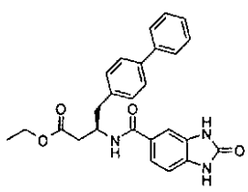
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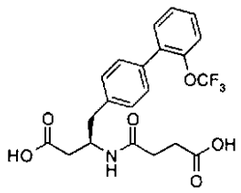
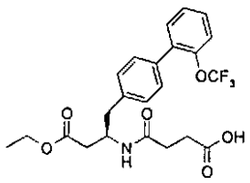
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
Ejemplo 5-52	 ácido R-4-(1-carboxi-3-(3'-(trifluoro-metoxi)-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico		NaOH acuoso, MeOH, rt	1.57 minutos. (D)	440.1
Ejemplo 5-53	 ácido (3R)-4-(3'-cloro-bifenil-4-il)-3-(5-oxo-pirrolidin-3-		NaOH acuoso, MeOH, rt	1.37 minutos. (D)	401.3

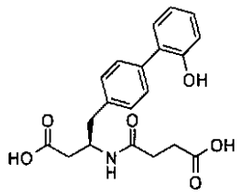
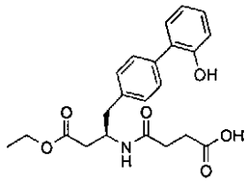
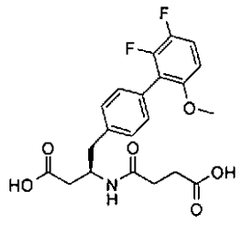
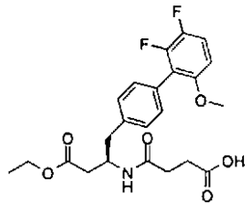
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
	carboxamido)-butanoico				
Ejemplo 5-54	 ácido R-4-(3'-cloro-bifenil-4-il)-3-(5-metil-1,3,4-oxadiazol-2-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.44 minutos. (D)	400.2
Ejemplo 5-55	 ácido R-4-(5'-fluoro-2'-metoxi-bifenil-4-il)-3-(3-		NaOH acuoso, MeOH, rt	1.37 minutos. (D)	415.1

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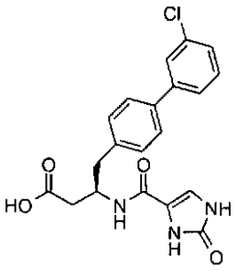
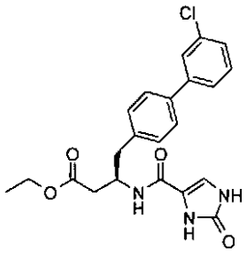
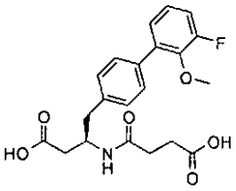
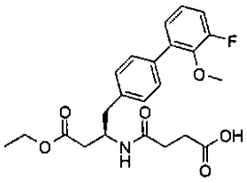
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
	hidroxi-isoxazol-5-carboxamido)-butanoico				
Ejemplo 5-56	 ácido R-4-(3'-cloro-bifenil-4-il)-3-(3-hidroxi-1H-pirazol-5-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.52 minutos. (D)	400.2
Ejemplo 5-57	 ácido R-4-(bifenil-4-il)-3-(5-oxo-4,5-		NaOH acuoso, MeOH, rt	1.77 minutos. (D)	368.2

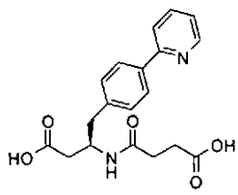
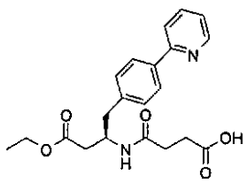
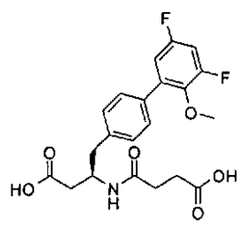
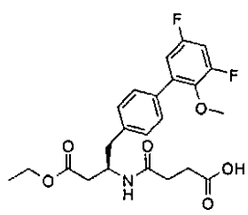
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
	dihidro-1,2,4-oxadiazol-3-carboxamido)-butanoico				
Ejemplo 5-58	 ácido R-4-(3'-cloro-bifenil-4-il)-3-(5-oxo-4,5-dihidro-1H-1,2,4-triazol-3-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.63 minutos. (D)	401.1
Ejemplo 5-59			NaOH acuoso, MeOH, rt	1.46 minutos. (D)	416.0

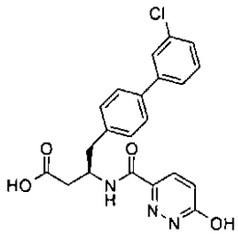
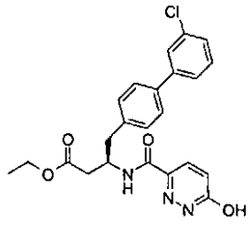
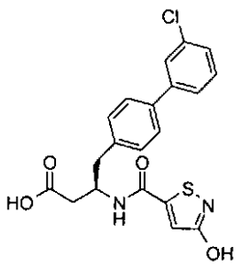
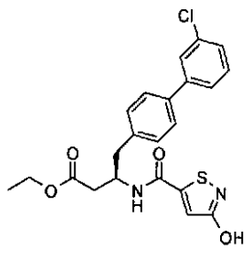
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
	ácido R-4-(bifenil-4-il)-3-(2-oxo-2,3-dihidro-1H-benzo-[d]-imidazol-5-carboxamido)-butanoico				
Ejemplo 5-60	 ácido R-4-(1-carboxi-3-(2'-(trifluoro-metoxi)-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico		NaOH acuoso, MeOH, rt	1.41 minutos. (D)	440.0

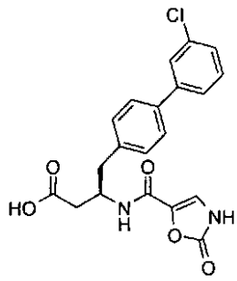
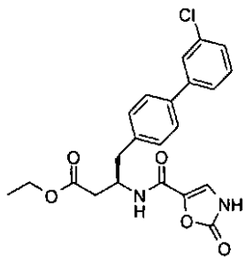
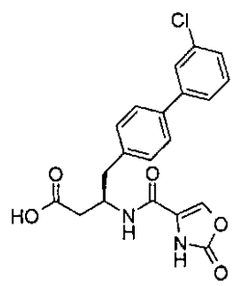
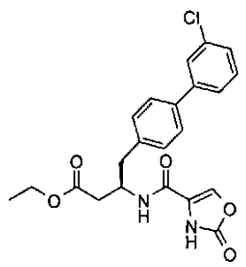
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
Ejemplo 5-61	 ácido R-4-(1-carboxi-3-(2'-hidroxi-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico		NaOH acuoso, MeOH, rt	1.16 minutos. (D)	372.2
Ejemplo 5-62	 ácido R-4-(1-carboxi-3-(2',3'-difluoro-6'-metoxi-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico		NaOH acuoso, MeOH, rt	1.34 minutos. (D)	422.2

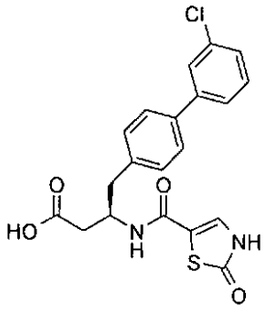
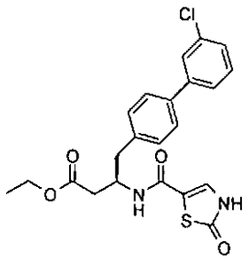
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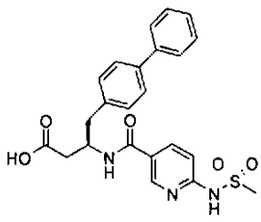
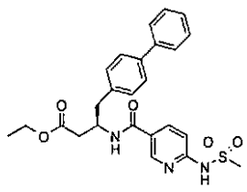
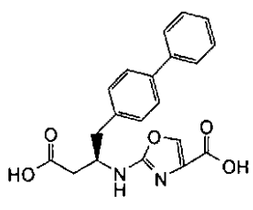
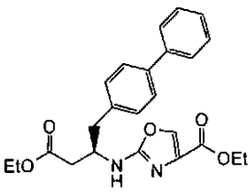
Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
Ejemplo 5-63	 ácido R-4-(3'-cloro-bifenil-4-il)-3-(2-oxo-2,3-dihidro-1H-imidazol-4-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.16 minutos. (D)	400.1
Ejemplo 5-64	 ácido R-4-(1-carboxi-3-(3'-fluoro-2'-metoxi-bifenil-4-il)-propan-2-il-		NaOH acuoso, MeOH, rt	1.29 minutos. (D)	404.1

Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
	amino)-4-oxo-butanoico				
Ejemplo 5-65	 ácido R-4-(1-carboxi-3-(4-piridin-2-il)-fenil)-propan-2-il-amino)-4-oxo-butanoico		NaOH acuoso, MeOH, rt	1.43 minutos. (D)	356.2
Ejemplo 5-66	 ácido R-4-(1-carboxi-3-(3',5'-difluoro-2'-metoxi-bifenil-4-il)-		NaOH acuoso, MeOH, rt	1.42 minutos. (D)	422.0

Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
	propan-2-il-amino)-4-oxo-butanoico				
Ejemplo 5-67	 ácido R-4-(3'-cloro-bifenil-4-il)-3-(6-hidroxi-piridazin-3-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.78 minutos. (D)	412.1
Ejemplo 5-68	 ácido R-4-(3'-cloro-bifenil-4-il)-		NaOH acuoso, MeOH, rt	1.53 minutos. (D)	417.1

Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
	3-(3-hidroxi-isotiazol-5-carboxamido)-butanoico				
Ejemplo 5-69	 ácido R-4-(3'-cloro-bifenil-4-il)-3-(2-oxo-2,3-dihidro-oxazol-5-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.79 minutos. (D)	401.2
Ejemplo 5-70			NaOH acuoso, MeOH, rt	1.62 minutos. (D)	401.1

Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
	ácido R-4-(3'-cloro-bifenil-4-il)-3-(2-oxo-2,3-dihidro-oxazol-4-carboxamido)-butanoico				
Ejemplo 5-71	 ácido R-4-(3'-cloro-bifenil-4-il)-3-(2-oxo-2,3-dihidro-tiazol-5-carboxamido)-butanoico		NaOH acuoso, MeOH, rt	1.73 minutos. (D)	417.2

Ejemplo #	Producto	Material de partida	Condición de Hidró-lisis	LCMS-RT (condi-ción)	MS (M+1)
Ejemplo 5-72	 ácido R-4-(bifenil-4-il)-3-(6-(metil-sulfonamido)-nicotinamido)-butanoico		NaOH acuoso, MeOH, rt	1.49 minutos. (D)	454.2
Ejemplo 5-73	 ácido 2-((R)-1-bifenil-4-il-metil-2-carboxi-etil-amino)-oxazol-4-carboxílico		NaOH acuoso, EtOH, rt	1.28 minutos. (A)	367.0

Ejemplo 5-38: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.65 (d, *J*=7.1 Hz, 2 H) 2.91 - 3.07 (m, 2 H) 3.26 (s, 3 H) 4.70 (m, 1 H) 7.04 (d, *J*=8.8 Hz, 1 H) 7.26 - 7.33 (m, 1 H) 7.33 - 7.44 (m, 3 H) 7.47 - 7.56 (m, 3 H) 7.57 (t, *J*=1.9 Hz, 1 H) 8.02 (dd, *J*=8.8, 2.5 Hz, 1 H) 8.55 (d, *J*=1.78 Hz, 1 H).

Ejemplo 5-39: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.36 - 2.60 (m, 6 H) 2.84 (dd, *J*=13.4, 6.1 Hz, 1 H) 2.91 (dd, *J*=13.4, 6.1 Hz, 1 H) 3.77 (s, 3 H) 4.34 - 4.58 (m, 1 H) 7.03 (d, *J*=8.6 Hz, 1 H) 7.18 - 7.31 (m, 4 H) 7.39 (d, *J*=8.1 Hz, 2 H)

Ejemplo 5-40: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.51 - 2.70 (m, 2 H) 2.79 - 2.99 (m, 2 H) 3.05 (s, 3 H) 4.41 - 4.62 (m, 1 H) 7.22 (d, *J*=8.8 Hz, 2 H) 7.33 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.43 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.56 - 7.66 (m, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 7.76 (d, *J*=8.6 Hz, 2 H) 8.30 (d, *J*=8.3 Hz, 1 H) 10.09 (s, 1 H) 12.24 (s, 1 H)

Ejemplo 5-41: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.28 (t, *J*=7.6 Hz, 3 H) 2.51 - 2.60 (m, 2 H) 2.84 - 2.94 (m, 2 H) 2.97 (q, *J*=7.6 Hz, 2 H) 4.36 - 4.56 (m, 1 H) 7.32 (d, *J*=8.3 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.60 - 7.66 (m, 3 H) 7.70 (t, *J*=1.8 Hz, 1 H) 8.23 (s, 1 H) 8.60 (d, *J*=8.3 Hz, 1 H) 12.30 (br. s., 1 H)

Ejemplo 5-42: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.23 - 2.31 (m, 2 H) 2.31 - 2.43 (m, 4 H) 2.76 (d, *J*=6.6 Hz, 2 H) 4.16 - 4.30 (m, 1 H) 6.87 - 7.02 (m, 2 H) 7.07 (dd, *J*=9.6, 3.0 Hz, 1 H) 7.21 (d, *J*=8.3 Hz, 2 H) 7.50 (d, *J*=8.1 Hz, 2 H) 7.90 (d, *J*=8.1 Hz, 1 H) 9.51 (br. s., 1 H)

Ejemplo 5-43: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.33 - 2.60 (m, 6 H) 2.85 (dd, *J*=13.7, 6.1 Hz, 1 H) 2.94 (dd, *J*=13.7, 6.1 Hz, 1 H) 3.45

(s, 3 H) 4.35 - 4.57 (m, 1 H) 7.14 (t, *J*=7.8 Hz, 1 H) 7.21 - 7.34 (m, 3 H) 7.38 (dd, *J*=8.0, 1.6 Hz, 1 H) 7.47 (d, *J*=8.3 Hz, 2 H)

Ejemplo 5-44: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.64 (d, *J*=5.8 Hz, 2 H) 3.01 (d, *J*=6.8 Hz, 2 H) 4.51 - 4.74 (m, 1 H) 7.00 (br. s., 1 H) 7.25 - 7.35 (m, 3 H) 7.40 (t, *J*=7.6 Hz, 2 H) 7.53 (d, *J*=8.1 Hz, 2 H) 7.58 (d, *J*=8.1 Hz, 2 H) 8.21 (br. s., 1 H)

Ejemplo 5-45: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.38 - 2.55 (m, 6 H) 2.85 (dd, *J*=13.6, 6.3, Hz, 1 H) 2.93 (dd, *J*=13.6, 6.3, Hz, 1 H) 4.40 - 4.56 (m, 1 H) 7.27 - 7.37 (m, 3 H) 7.40 (t, *J*=7.8 Hz, 1 H) 7.54 - 7.56 (m, 3 H) 7.60 (t, *J*=1.8 Hz, 1 H)

Ejemplo 5-46: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.51 - 2.63 (m, 2 H) 2.84 (dd, *J*=13.6, 8.3 Hz, 1 H) 2.89 (dd, *J*=13.6, 8.3 Hz, 1 H) 4.40 - 4.55 (m, 1 H) 7.30 (d, *J*=8.3 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.58 - 7.66 (m, 3 H) 7.70 (t, *J*=1.9 Hz, 1 H) 8.95 (d, *J*=8.6 Hz, 1 H) 12.93 (s, 1 H)

Ejemplo 5-47: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.25 (t, *J*=7.6 Hz, 3 H) 2.51 - 2.59 (m, 2 H) 2.80 (q, *J*=7.6 Hz, 2 H) 2.84 - 2.94 (m, 2 H) 4.41 - 4.56 (m, 1 H) 7.31 (d, *J*=8.1 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.59 (s, 1 H) 7.63 (d, *J*=8.3 Hz, 3 H) 7.70 (t, *J*=1.9 Hz, 1 H) 8.45 (d, *J*=8.6 Hz, 1 H) 12.27 (br. s., 1 H)

Ejemplo 5-48: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.33 (t, *J*=7.6 Hz, 3 H) 2.64 (d, *J*=6.8 Hz, 2 H) 2.84 (q, *J*=7.6 Hz, 2 H) 2.98 (d, *J*=7.01 Hz, 2 H) 3.72 (s, 3 H) 4.62 - 4.75 (m, 1 H) 6.94 - 7.06 (m, 3 H) 7.27 (d, *J*=8.1 Hz, 2 H) 7.40 (d, *J*=8.3 Hz, 2 H) 7.54 (s, 1 H)

Ejemplo 5-49: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.51 - 2.62 (m,

2 H) 2.84 (dd, *J*=13.7, 7.9 Hz, 1 H) 2.91 (dd, *J*=13.7, 7.9 Hz, 1 H) 3.73 (s, 3 H) 4.42 - 4.55 (m, 1 H) 7.05 - 7.19 (m, 3 H) 7.25 (d, *J*=8.1 Hz, 2 H) 7.42 (d, *J*=8.1 Hz, 2 H) 7.73 (s, 1 H) 8.55 (s, 1 H) 8.63 (d, *J*=8.6 Hz, 1 H)

Ejemplo 5-50: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.69 (d, *J*=6.8 Hz, 2 H) 2.95 - 3.10 (m, 2 H) 4.68 - 4.79 (m, 1 H) 7.21 - 7.33 (m, 1 H) 7.33 - 7.47 (m, 4 H) 7.49 - 7.65 (m, 4 H) 7.76 - 7.97 (m, 2 H) 8.20 - 8.42 (m, 1 H)

Ejemplo 5-51: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.62 (d, *J*=6.6 Hz, 2 H) 2.96 (d, *J*=7.3 Hz, 2 H) 4.54 - 4.68 (m, 1 H) 7.28 - 7.36 (m, 3 H) 7.40 (t, *J*=7.7 Hz, 2 H) 7.56 (dd, *J*=17.2, 7.8 Hz, 4 H)

Ejemplo 5-52: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.34 - 2.45 (m, 2 H) 2.45 - 2.59 (m, 4 H) 2.86 (dd, *J*=13.4, 6.0 Hz, 1 H) 2.93 (dd, *J*=13.4, 6.0 Hz, 1 H) 4.40 - 4.55 (m, 1 H) 7.19 - 7.26 (m, 1 H) 7.34 (d, *J*=8.1 Hz, 2 H) 7.46 - 7.49 (m, 1 H) 7.51 (t, *J*=8.0 Hz, 1 H) 7.56 (d, *J*=8.3 Hz, 2 H) 7.61 (d, *J*=7.8 Hz, 1 H)

Ejemplo 5-53: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.04 - 2.26 (m, 2 H) 2.31 - 2.46 (m, 2 H) 2.69 - 2.88 (m, 2 H) 2.94 - 3.21 (m, 2 H) 4.18 - 4.37 (m, 1 H) 7.28 (d, *J*=7.1 Hz, 2 H) 7.35 - 7.43 (m, 1 H) 7.43 - 7.54 (m, 2 H) 7.63 (d, *J*=8.2 Hz, 3 H) 7.70 (t, *J*=1.9 Hz, 1 H) 7.98 (dd, *J*=8.3, 2.3 Hz, 1 H) 12.22 (br. s., 1 H)

Ejemplo 5-54: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.57 (s, 3 H) 2.68 (d, *J*=6.6 Hz, 2 H) 2.92 - 3.08 (m, 2 H) 4.64 - 4.74 (m, 1 H) 7.25 - 7.33 (m, 1 H) 7.33 - 7.44 (m, 3 H) 7.44 - 7.55 (m, 3 H) 7.57 (t, *J*=1.8 Hz, 1 H)

Ejemplo 5-55: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.64 (d, *J*=6.3 Hz, 2 H) 2.97 (d, *J*=7.1 Hz, 2 H) 3.74 (s, 3 H) 4.58 - 4.73 (m, 1 H) 6.43 (s, 1 H) 6.96 - 7.08 (m, 3 H) 7.27 (d, *J*=8.1 Hz, 2 H) 7.42 (d, *J*=8.1 Hz, 2 H) 8.71 (d, *J*=8.3 Hz, 1 H)

Ejemplo 5-56: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.52 - 2.67 (m, 2 H) 2.80 - 2.96 (m, 2 H) 4.38 - 4.54 (m, 1 H) 5.90 (br. s., 1 H) 7.30 (d, *J*=8.1 Hz, 2 H) 7.35 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.61 (d, *J*=8.3 Hz, 3 H) 7.69 (t, *J*=1.9 Hz, 1 H) 8.08 (br. s., 1 H)

Ejemplo 5-57: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.48 - 2.55 (m, 1 H) 2.64 (d, *J*=6.8 Hz, 1 H) 2.88 - 3.00 (m, 2 H) 4.32 - 4.69 (m, 1 H) 7.26 - 7.35 (m, 3 H) 7.41 (t, *J*=7.5 Hz, 2 H) 7.49 - 7.65 (m, 4 H)

Ejemplo 5-58: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.62 (d, *J*=6.6 Hz, 2 H) 2.92 - 3.01 (m, 2 H) 4.59 - 4.64 (m, 1 H) 7.28 - 7.43 (m, 4 H) 7.48 - 7.56 (m, 3 H) 7.59 (t, *J*=1.9 Hz, 1 H)

Ejemplo 5-59: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.64 (d, *J*=6.6 Hz, 2 H) 3.01 (d, *J*=7.1 Hz, 2 H) 4.63 - 4.75 (m, 1 H) 7.05 (d, *J*=8.1 Hz, 1 H) 7.26 - 7.32 (m, 1 H) 7.35 (d, *J*=8.3 Hz, 2 H) 7.37 - 7.43 (m, 2 H) 7.44 (d, *J*=1.0 Hz, 1 H) 7.48 (dd, *J*=8.1, 1.77 Hz, 1 H) 7.52 - 7.60 (m, 4 H)

Ejemplo 5-60: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.30 - 2.44 (m, 2 H) 2.44 - 2.64 (m, 4 H) 2.87 (dd, *J*=13.7, 6.4 Hz, 1 H) 2.95 (dd, *J*=13.7, 6.4 Hz, 1 H) 4.42 - 4.53 (m, 1 H) 7.27 - 7.52 (m, 8 H)

Ejemplo 5-61: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.22 - 2.32 (m, 2 H) 2.32 - 2.44 (m, 4 H) 2.76 (d, *J*=6.6 Hz, 2 H) 4.16 - 4.29 (m, 1 H) 6.82 - 6.88 (m, 1 H) 6.89 - 6.97 (m, 1 H) 7.08 - 7.17 (m, 1 H) 7.17 -

7.28 (m, 3 H) 7.47 (d, *J*=8.1 Hz, 2 H) 7.90 (d, *J*=8.1 Hz, 1 H) 9.47 (br. s., 1 H) 12.14 (br. s., 1 H)

Ejemplo 5-62: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.22 - 2.31 (m, 2 H) 2.33 - 2.42 (m, 4 H) 2.72 - 2.85 (m, 2 H) 3.72 (s, 3 H) 4.16 - 4.34 (m, 1 H) 6.92 (ddd, *J*=9.4, 3.79, 1.8 Hz, 1 H) 7.21 - 7.33 (m, 4 H) 7.34 - 7.45 (m, 1 H) 7.92 (d, *J*=8.1 Hz, 1 H) 12.14 (br. s., 2 H)

Ejemplo 5-63: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.42 - 2.48 (m, 2 H) 2.85 (d, *J*=6.8 Hz, 2 H) 4.30 - 4.46 (m, 1 H) 6.99 (s, 1 H) 7.30 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.42 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.63 (d, *J*=8.1 Hz, 3 H) 7.67 - 7.77 (m, 2 H) 10.13 (br. s., 1 H) 10.22 (br. s., 1 H) 12.26 (br. s., 1 H)

Ejemplo 5-64: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.35 - 2.60 (m, 6 H) 2.85 (dd, *J*=13.7, 6.4 Hz, 1 H) 2.93 (dd, *J*=13.7, 6.4 Hz, 1 H) 3.65 (s, 3 H) 4.37 - 4.58 (m, 1 H) 7.05 - 7.18 (m, 3 H) 7.30 (d, *J*=8.1 Hz, 2 H) 7.44 (d, *J*=8.3 Hz, 2 H)

Ejemplo 5-65: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.38 - 2.56 (m, 6 H) 2.85 (dd, *J*=13.4, 7.3 Hz, 1 H) 2.89 (dd, *J*=13.4, 7.3 Hz, 1 H) 4.40 - 4.52 (m, 1 H) 7.26 - 7.35 (m, 3 H) 7.36 - 7.46 (m, 2 H) 7.52 - 7.61 (m, 3 H)

Ejemplo 5-66: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.31 - 2.58 (m, 6 H) 2.68 - 2.99 (m, 2 H) 3.63 (s, 3 H) 4.33 - 4.56 (m, 1 H) 6.92 - 7.18 (m, 3 H) 7.30 - 7.38 (m, 1 H) 7.38 - 7.46 (m, 2 H)

Ejemplo 5-67: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.51 - 2.65 (m, 2 H) 2.86 (dd, *J*=13.7, 8.1 Hz, 1 H) 2.95 (dd, *J*=13.7, 8.1 Hz, 1 H) 4.42 - 4.61 (m, 1 H) 6.89 - 6.99 (m, 1 H) 7.30 (d, *J*=8.3 Hz, 2 H) 7.37

- 7.42 (m, 1 H) 7.42 - 7.51 (m, 1 H) 7.62 (d, *J*=8.1 Hz, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 7.76 (d, *J*=9.9 Hz, 1 H) 8.41 (d, *J*=9.1 Hz, 1 H) 12.26 (br. s., 1 H) 13.40 (s, 1 H)

Ejemplo 5-68: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.51 - 2.57 (m, 2 H) 2.90 (d, *J*=6.8 Hz, 2 H) 4.34 - 4.52 (m, 1 H) 7.15 (s, 1 H) 7.31 (d, *J*=8.1 Hz, 2 H) 7.39 (dd, *J*=7.6, 1.77 Hz, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.59 - 7.66 (m, 3 H) 7.70 (t, *J*=1.8 Hz, 1 H) 8.74 (d, *J*=8.6 Hz, 1 H)

Ejemplo 5-69: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.61 (d, *J*=6.6 Hz, 2 H) 2.89 - 3.02 (m, 2 H) 4.53 - 4.71 (m, 1 H) 7.16 - 7.37 (m, 4 H) 7.39 (t, *J*=7.8 Hz, 1 H) 7.45 - 7.57 (m, 3 H) 7.59 (t, *J*=1.8 Hz, 1 H) 8.20 (d, 1 H).

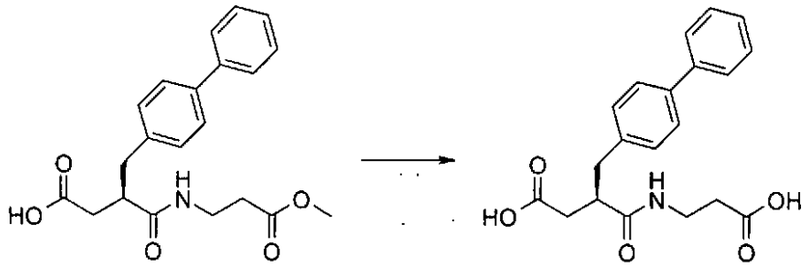
Ejemplo 5-70: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.41 - 2.57 (m, 2 H) 2.73 - 2.96 (m, 2 H) 4.35 - 4.46 (m, 1 H) 7.30 (d, *J*=8.3 Hz, 2 H) 7.35 - 7.44 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.57 - 7.67 (m, 4 H) 7.70 (t, *J*=1.9 Hz, 1 H) 8.23 (d, *J*=8.3 Hz, 1 H) 11.14 (s, 1 H) 12.29 (br. s., 1 H).

Ejemplo 5-71: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.58 (dd, *J*=6.8, 1.8 Hz, 2 H) 2.95 (dd, *J*=7.0, 3.4 Hz, 2 H) 4.53 - 4.66 (m, 1 H) 7.27 - 7.36 (m, 3 H) 7.36-7.43 (m, 2H), 7.49-7.57 (m, 3H) 7.59 (t, *J*=1.7 Hz, 1 H).

Ejemplo 5-72: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.60 - 2.71 (m, 2 H), 3.03 (dd, *J*=6.9, 4.7 Hz, 2 H), 3.28 (s, 3 H), 4.65 - 4.76 (m, 1 H), 7.06 (d, *J*=8.8 Hz, 1 H), 7.23 - 7.38 (m, 3 H), 7.38 - 7.47 (m, 2 H), 7.50 - 7.64 (m, 5 H), 8.03 (dd, *J*=8.8, 2.3 Hz, 1 H), 8.17 (d, 1 H), 8.56 (br. s., 1 H).

Ejemplo 5-73: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.43 - 2.59 (m, 2 H), 2.82 - 2.95 (m, 2 H), 4.04 - 4.16 (m, 1 H), 7.30 (d, J=8.3 Hz, 2 H), 7.34 (t, J=7.3 Hz, 1 H), 7.45 (t, J=7.6 Hz, 2 H), 7.59 (d, J=8.1 Hz, 3 H), 7.64 (d, J=8.6 Hz, 2 H), 8.03 (s, 1 H), 12.45 (br. s., 2 H).

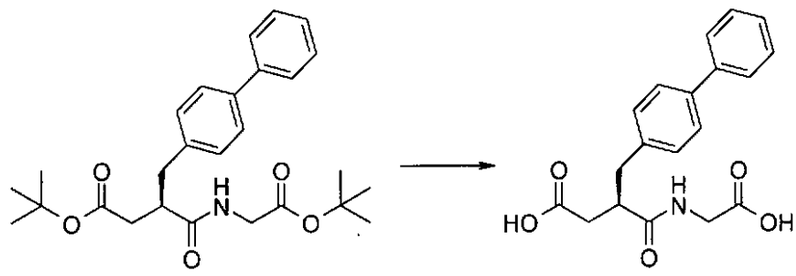
Ejemplo 6-1: Síntesis de ácido (R)-3-(bifenil-4-il-metil)-4-(2-carboxi-etil-amino)-4-oxo-butanoico



A una solución del ácido (R)-3-(bifenil-4-il-metil)-4-(3-metoxi-3-oxopropil-amino)-4-oxo-butanoico (22.1 miligramos, 0.060 milimoles) en tetrahidrofurano (0.6 mililitros), y metanol (0.1 mililitros), se le agrega NaOH acuoso 1M (0.12 mililitros, 0.12 milimoles) a temperatura ambiente. Después de agitar durante 3 horas, se agrega NaOH acuoso 1M adicional (0.12 mililitros, 0.12 milimoles). La mezcla de reacción se deja agitándose durante 30 minutos, y se apaga con 0.5 mililitros de HCl acuoso 1M y 0.5 mililitros de salmuera. La mezcla se extrae dos veces con acetato de etilo, y la capa orgánica se concentra bajo presión reducida, para dar el ácido (R)-3-(bifenil-4-il-metil)-4-(2-carboxi-etil-amino)-4-oxo-butanoico (16.4 miligramos). HPLC - tiempo de retención = 1.04 minutos (condición A); MS (m+1) = 356.1; ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.13-2.31 (m, 3 H) 2.59 - 2.65 (m, 1 H) 2.81 - 2.90 (m, 2 H) 3.12

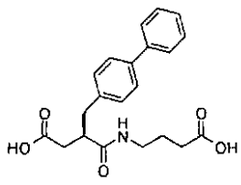
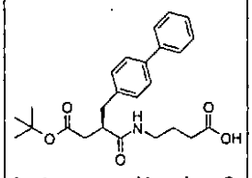
- 3.27 (m, 2 H) 7.26 (d, 2 H, J = 8 Hz) 7.34 (t, 1 H, J = 7.4 Hz) 7.45 (t, 2 H, J = 7.7 Hz) 7.57 (d, 2 H, J = 8.1 Hz) 7.63-7.65.

Ejemplo 7-1: Síntesis de ácido (R)-3-bifenil-4-il-metil-N-carboxi-metil-succinámico



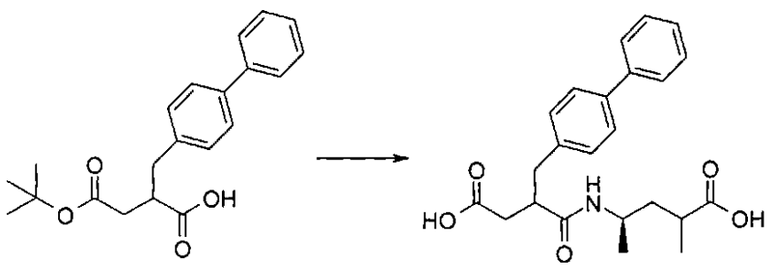
Una solución del 3-(bifenil-4-il-metil)-4-(2-terbutoxi-2-oxo-etil-amino)-4-oxo-butanoato de (R)-terbutilo (40 miligramos, 0.088 milimoles), y ácido trifluoro-acético (0.5 mililitros, 6.49 milimoles) en dicloro-metano (1.5 mililitros) se deja agitándose durante 2 horas a temperatura ambiente. La reacción se concentra bajo presión reducida, y el residuo obtenido se suspende en dicloro-metano (0.5 mililitros) y heptano (2 mililitros), y se recolecta en un embudo, dando el ácido (R)-3-bifenil-4-il-metil-N-carboxi-metil-succinámico (9.6 miligramos). HPLC - tiempo de retención = 1.26 minutos (condición A); MS (m+1) = 342.0; ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39 (dd, J=16.67, 5.31 Hz, 1 H) 2.63 - 2.82 (m, 2 H) 2.98 - 3.14 (m, 2 H) 3.84 y 3.95 (AB, 2 H, J = 17.8 Hz) 7.26 - 7.33 (m, 3 H) 7.40 (t, J=7.71 Hz, 2 H) 7.56 (dd, J=19.96, 8.08 Hz, 4 H).

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 7-1:

Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 7-2	 ácido (R)-3-bifenil-4-il-metil-N-(3-carboxi-propil)-succinámico	 Intermediario 3	TFA, DCM, rt	1.35 minutos. (A)	370.0

Ejemplo 7-2: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1.51-1.58 (m, 2 H) 2.12 - 2.21 (m, 3 H) 2.49- 2.65 (m, 2 H) 2.81 - 2.89 (m, 2 H) 2.94 - 3.08 (m, 2 H) 7.26 (d, 2 H, J = 8.1 Hz) 7.32 - 7.36 (m, 1 H) 7.43-7.46 (m, 2 H) 7.57 (d, 2 H, J = 8.0 Hz) 7.63-7.65 (m, 2H).

Ejemplo 8-1: Síntesis de ácido (R)-4-(2-bifenil-4-il-metil-3-carboxi-propionil-amino)-2-metil-pentanoico



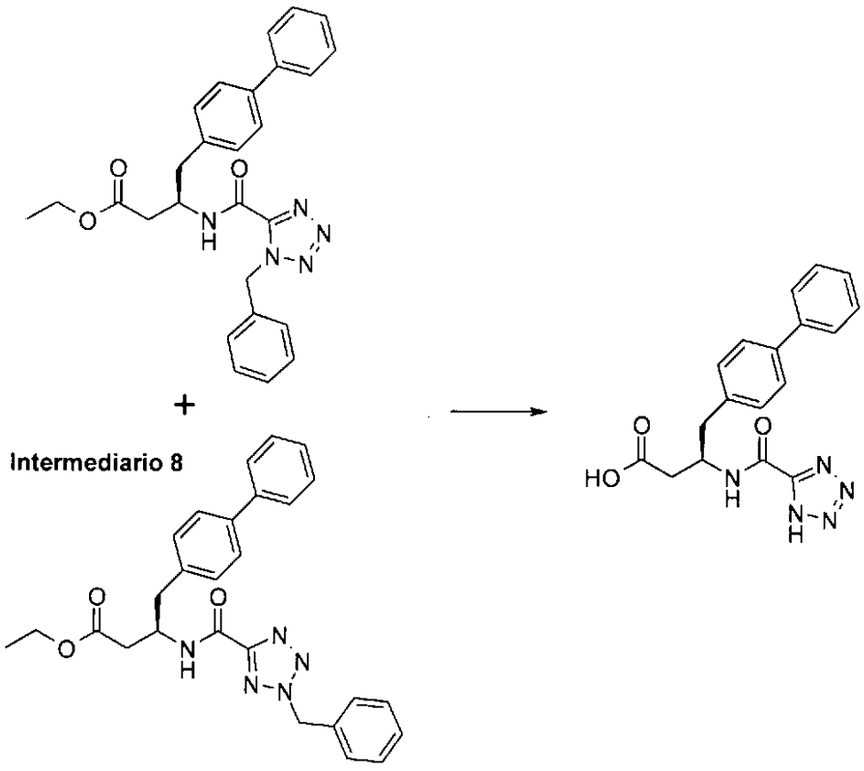
Intermediario 10

A una solución agitada de 4-terbutil-éster del ácido 2-bifenil-4-il-metil-succínico (100 miligramos, 0.29 milimoles) en N,N-dimetil-formamida (10 mililitros), se le agregan HOBt (45 miligramos, 0.29 milimoles), y 1-etil-3-(3'-dimetil-amino-propil)-carbodi-imida (56 miligramos, 0.29 milimoles), y la mezcla se agita a temperatura ambiente durante 10 minutos; entonces se agregan trifluoro-acetato de etil-éster del ácido (2R,4R)-4-amino-2-metil-pentanoico (47 miligramos, 0.29 milimoles), y trietil-amina (89 miligramos, 0.87 milimoles), y la mezcla se agita a temperatura ambiente durante 5 horas. La mezcla se apaga con agua, y se extrae con acetato de etilo. La capa orgánica se lava con agua, salmuera, se seca sobre sulfato de magnesio y se filtra. El solvente se remueve bajo presión reducida, para dar 1-etil-éster de 9-terbutil-éster del ácido (2R,4R)-7-bifenil-4-il-metil-2,4-dimetil-6-oxo-nonanodioico.

En seguida, a una solución del 1-etil-éster de 9-terbutil-éster del ácido (2R,4R)-7-bifenil-4-il-metil-2,4-dimetil-6-oxo-nonanodioico EtOH (4 mililitros), se le agrega NaOH acuoso 1M (4 mililitros), y la mezcla se agita a temperatura ambiente durante 30 minutos. La mezcla se acidifica a un pH de 2 a 3 con HCl acuoso 1M, y se extrae con acetato de etilo. El solvente se remueve bajo presión reducida, y el residuo se purifica mediante HPLC de preparación utilizando un gradiente del 10 al 100 por ciento de MeCN/agua (ácido trifluoro-acético al 0.1 por ciento). La liofilización de las fracciones apropiadas proporciona el ácido (R)-4-(2-bifenil-4-il-metil-3-carboxi-propionil-amino)-2-metil-pentanoico. HPLC - tiempo de retención =

1.13 minutos (condición C); MS 398.2 (M+1); ^{1}H- RMN (400 MHz, DMSO-d6) δ ppm 0.93 (m, 6H), 1.23 (m, 1H), 1.59 (m, 1H), 2.17 (m, 1H), 2.63 (m, 1H), 2.82 (m, 1H), 3.72 (m, 1H), 7.27 (m, 2H), 7.33 (m, 1H), 7.45 (m, 2H), 7.56 (m, 2H), 7.62 (m, 2H), 7.71 (m, 1H), 12.07 (s, 1H).

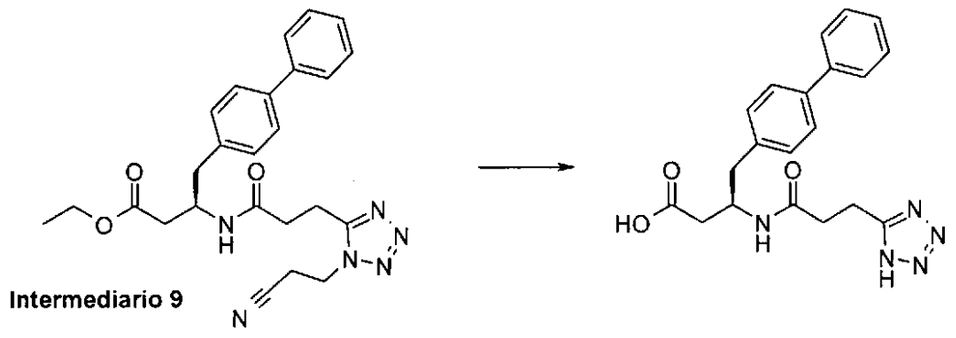
Ejemplo 9-1: Síntesis de ácido (R)-4-bifenil-4-il-3-[(1H-tetrazol-5-carbonil)-amino]-butírico



A una mezcla del etil-éster del ácido (R)-3-[(1-bencil-1H-tetrazol-5-carbonil)-amino]-4-bifenil-4-il-butírico y el etil-éster del ácido (R)-3-[(2-bencil-2H-tetrazol-5-carbonil)-amino]-4-bifenil-4-il-butírico (180 miligramos, 0.383 milimoles) en EtOH (1 mililitro) y tetrahidrofurano (1 mililitro), se le agrega LiOH acuoso 1M (2

mililitros). Después de agitar durante 0.5 horas, la mezcla de reacción se acidifica con HCl 1M acuoso. La mezcla se extrae con acetato de etilo, se seca sobre Na_2SO_4, y se concentra bajo presión reducida. El residuo se disuelve en metanol, y se hidrogena con Pd/C al 10 por ciento a temperatura ambiente durante 3 horas, y a 40°C durante 2 horas. La mezcla de reacción se concentra y se purifica mediante HPLC en fase inversa para dar el ácido (R)-4-bifenil-4-il-3-[(1H-tetrazol-5-carbonil)-amino]-butírico. HPLC - tiempo de retención = 1.18 minutos (condición D); MS (m+1) = 352; ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.56 (dd, J=5.81, 15.92Hz, 1H), 2.67 (dd, J=7.58, 15.92Hz, 1H), 2.85-2.99 (m, 2H), 4.55-4.64 (m, 1H), 7.26-7.35 (m, 3H), 7.43 (dd, J=7.83, 7.83Hz, 2H), 7.56 (d, J=8.08Hz, 2H), 7.62 (d, J=7.07Hz, 2H), 9.28 (d, 8.84Hz, 1H), 12.28 (s, 1H).

Ejemplo 10-1: ácido (R)-4-bifenil-4-il-3-(3-1H-tetrazol-5-il-propionil-amino)-butírico



Intermediario 9

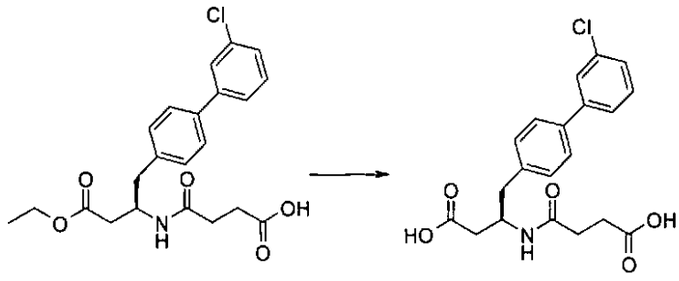
A una solución del etil-éster del ácido (R)-4-bifenil-4-il-3-{3-[1-(2-ciano-etil)-1H-tetrazol-5-il]-propionil-amino}-butírico (137 miligramos, 0.297 milimoles) en dicloro-metano (8 mililitros) a temperatura ambiente, se le agrega DBU (1.507 mililitros, 10.00

milimoles), y la mezcla se agita a temperatura ambiente durante 2 horas. La reacción se extrae con dicloro-metano. La capa orgánica combinada se lava con NH_4Cl saturado, salmuera, y se seca sobre sulfato de sodio anhidro, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía por evaporación instantánea (gel de sílice, del 2 por ciento al 10 por ciento de EtOH/DCM), para dar el etil-éster del ácido (R)-4-bifenil-4-il-3-(3-1H-tetrazol-5-il-propionil-amino)-butírico (37 miligramos). Al éster obtenido en EtOH (2 mililitros) a temperatura ambiente, se le agrega NaOH acuoso 1M (1 mililitro, 1.0 milimoles), y la mezcla se agita a temperatura ambiente durante 1 hora. A la reacción se le agrega 1 mililitro de HCl acuoso 1M hasta un pH = 4, y la mezcla se purifica mediante HPLC en fase inversa [del 30 por ciento al 60 por ciento de acetonitrilo-H_2O (ácido trifluoro-acético al 0.1 por ciento)], para dar el ácido (R)-4-bifenil-4-il-3-(3-1H-tetrazol-5-il-propionil-amino)-butírico. HPLC - tiempo de retención = 1.24 minutos (condición C); MS (m+1) = 380; ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.37 (dd, *J*=6.7, 2.1 Hz, 2 H), 2.53 (t, *J*=7.6 Hz, 2 H), 2.69 - 2.82 (m, 2 H), 3.02 (t, *J*=7.7 Hz, 2 H), 4.17 - 4.29 (m, 1 H), 7.22 (d, *J*=8.3 Hz, 2 H), 7.34 (tt, *J*=7.3, 1.3 Hz, 1 H), 7.42 - 7.48 (m, 2 H), 7.57 (d, *J*=8.3 Hz, 2 H), 7.64 (dd, *J*=8.2, 1.1 Hz, 2 H), 8.00 (d, *J*=8.1 Hz, 1 H), 12.21 (br. s., 1 H), 15.92 (br. s., 1 H).

HPLC quiral - tiempo de retención = 5.64 minutos. Columna: Daicel CHIRALCEL OJ-H (4.6 x 100 milímetros); velocidad de flujo = 1 mililitro/minuto.; eluyente: EtOH (que contiene ácido trifluoro-

acético al 0.1 por ciento)/heptano = 2/8.

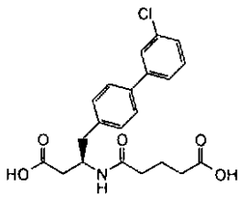
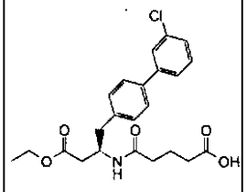
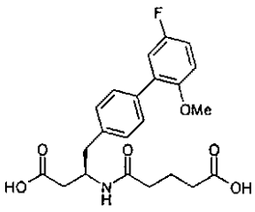
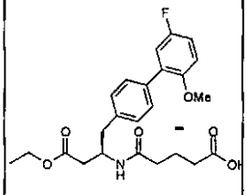
Ejemplo 11-1: Síntesis de ácido (R)-4-(1-carboxi-3-(3'-cloro-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico

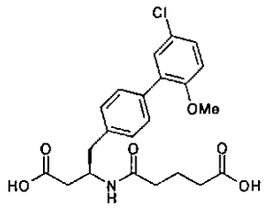
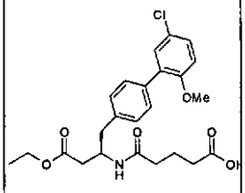
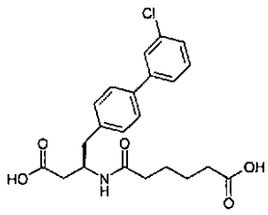
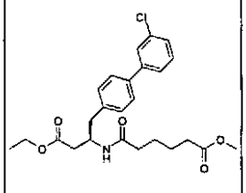


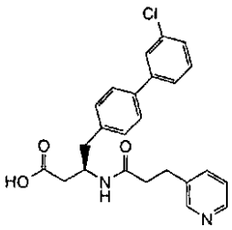
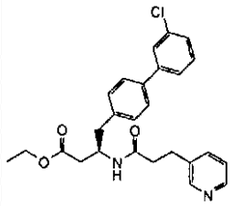
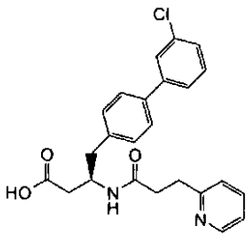
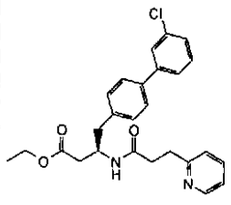
A una solución del ácido (R)-4-(1-(bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico (110 miligramos, 0.263 milimoles) en tetrahidrofurano (2 mililitros) y metanol (0.2 mililitros), se le agrega una solución acuosa de NaOH 1M (1.053 mililitros, 1.053 milimoles) a temperatura ambiente. Después de agitar durante 1 hora, la reacción se apaga con HCl acuoso 0.1 M, y la solución se diluye con dicloro-metano (15 mililitros), y se deja agitándose durante 1.5 horas. El sólido precipitado se recolecta en un embudo, se lava con agua, DCM, heptano, y entonces dicloro-metano, en ese orden, y se seca bajo presión reducida hasta dar el ácido (R)-4-(1-carboxi-3-(3'-cloro-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico (66 miligramos). HPLC - tiempo de retención = 0.87 minutos (condición B); MS (m+1) = 390.0; ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39-2.55 (m, 6 H) 2.86 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.6 Hz, 1 H) 2.92 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.2 Hz, 1 H) 4.42 - 4.49 (m, 1 H) 7.30 - 7.34 (m, 3 H) 7.40 (t, J = 7.4 Hz, 1 H) 7.51 - 7.56 (m, 3 H) 7.60 (t, J = 1.8 Hz, 1 H).

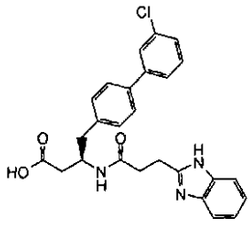
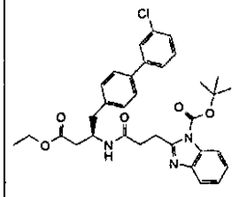
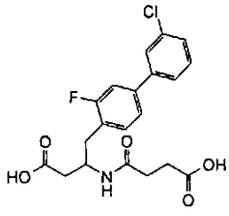
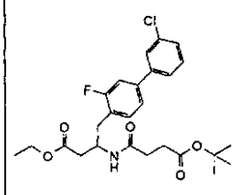
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Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 11-1:

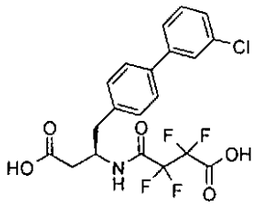
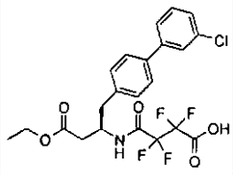
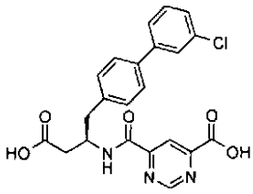
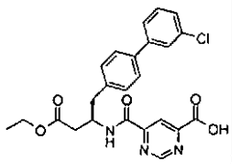
Ejemplo #	Producto	Material de partida	Condición de hidrólisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 11-2	 ácido (R)-5-(1-carboxi-3-(3'-cloro-bifenil-4-il)-propan-2-il-amino)-5-oxo-pentanoico		NaOH acuoso, tetrahidrofurano, MeOH, RT	0.79 minutos. (B)	404.1
Ejemplo 11-3	 ácido (R)-5-(1-carboxi-3-(5'-fluoro-2'-metoxi-bifenil-4-il)-propan-2-il-		NaOH acuoso, tetrahidrofurano, MeOH, RT	0.65 minutos. (B)	418.2

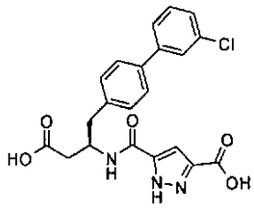
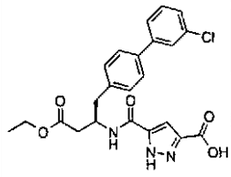
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	amino)-5-oxo-pentanoico				
Ejemplo 11-4	 ácido (R)-5-(1-carboxi-3-(5'-cloro-2'-metoxi-bifenil-4-il)-propan-2-il-amino)-5-oxo-pentanoico		NaOH acuoso, tetra-hidro-furano, MeOH, RT	0.63 minutos. (B)	434.3
Ejemplo 11-5	 ácido (R)-6-(1-carboxi-3-(3'-cloro-bifenil-4-il)-		NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.40 minutos. (A)	418.3

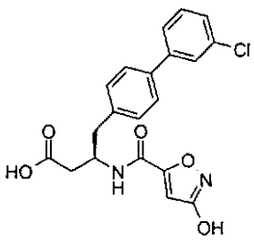
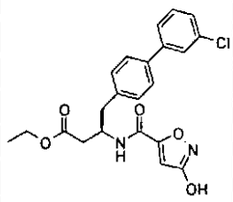
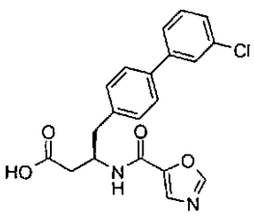
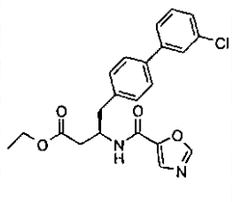
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	propan-2-il-amino)-6-oxo-hexanoico				
Ejemplo 11-6	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-(3-(piridin-3-il)-propanamido)-butanoico		NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.40 minutos. (A)	423.3
Ejemplo 11-7	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-(3-(piridin-2-il)-		NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.39 minutos. (A)	423.3

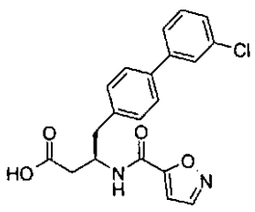
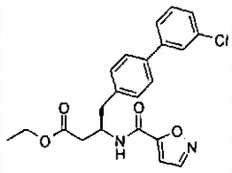
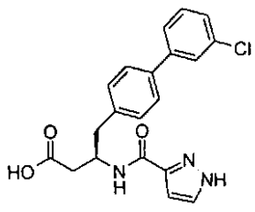
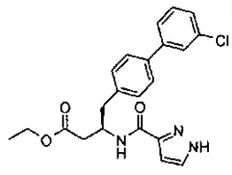
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	propanamido)-butanoico				
Ejemplo 11-9	 ácido (R)-3-(3-(1H-benzo-[d]-imidazol-2-il)-propanamido)-4-(3'-cloro-bifenil-4-il)-butanoico		NaOH acuoso, tetra-hidro-furano, MeOH, RT	1.50 minutos. (B)	462.3
Ejemplo 11-10	 ácido 4-(1-carboxi-3-(3'-cloro-3-fluoro-bifenil-4-il)-		NaOH acuoso, tetra-hidro-furano, MeOH, 50°C	0.72 minutos. (B)	408.2

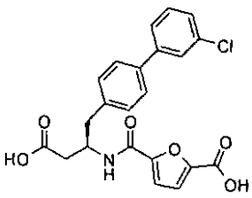
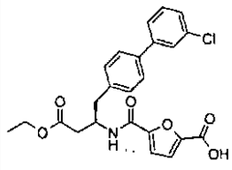
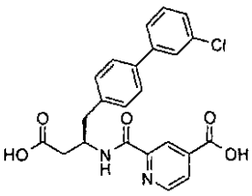
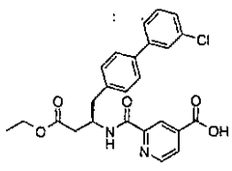
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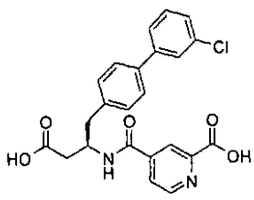
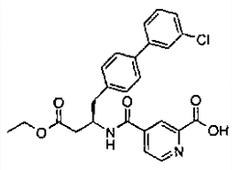
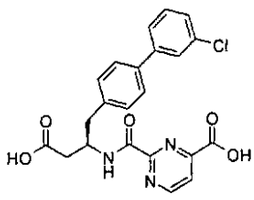
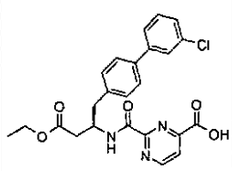
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	propan-2-il-amino)-4-oxo-butanoico				
Ejemplo 11-11	 ácido N-[(R)-2-carboxi-1-(3'-cloro-bifenil-4-il-metil)-etil]-2,2,3,3-tetrafluoro-succinámico		NaOH acuoso, EtOH, rt	1.16 minutos. (C)	462.2
Ejemplo 11-12	 ácido 6-[(R)-2-carboxi-1-(3'-		NaOH acuoso, EtOH, rt	1.34 minutos. (C)	440.2

Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	cloro-bifenil-4-il-metil)-etil-carbamoil]-pirimidin-4-carboxílico				
Ejemplo 11-13	 ácido 5-[(R)-2-carboxi-1-(3'-cloro-bifenil-4-il-metil)-etil-carbamoil]-1H-pirazol-3-carboxílico		NaOH acuoso, EtOH, 50°C	1.09 minutos. (C)	428.2

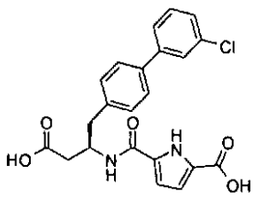
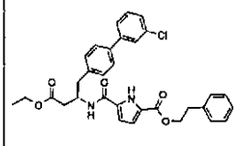
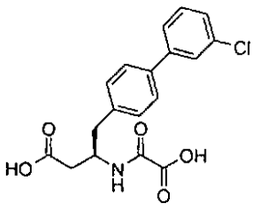
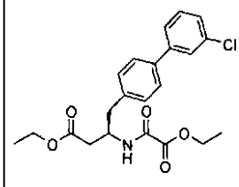
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 11-14	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(3-hidroxi-isoxazol-5-carbonil)-amino]-butírico		NaOH acuoso, EtOH, rt	1.17 minutos. (C)	401.0
Ejemplo 11-15	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(oxazol-5-carbonil)-amino]-butírico		NaOH acuoso, EtOH, rt	1.12 minutos. (C)	385.2

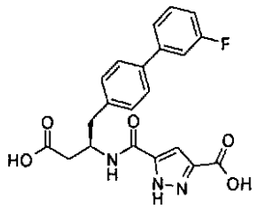
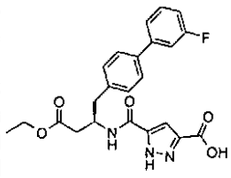
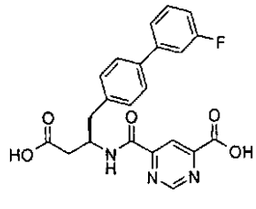
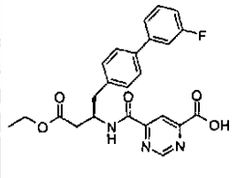
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 11-16	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(isoxazol-5-carbonil)-amino]-butírico		BCl_3, DCM, rt	1.15 minutos. (C)	385.1
Ejemplo 11-17	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(1H-pirazol-3-carbonil)-amino]-butírico		NaOH acuoso, EtOH, 50°C	1.18 minutos. (C)	384.3

Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 11-18	 ácido 5-[(R)-2-carboxi-1-(3'-cloro-bifenil-4-il-metil)-etil-carbamoil]-furan-2-carboxílico		NaOH acuoso, EtOH, 50°C	1.08 minutos. (C)	428.2
Ejemplo 11-19	 ácido 2-[(R)-2-carboxi-1-(3'-cloro-bifenil-4-il-metil)-etil-carbamoil]-isonicotínico		NaOH acuoso, EtOH, rt	1.04 minutos. (C)	439.3

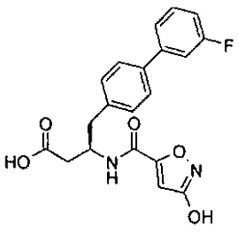
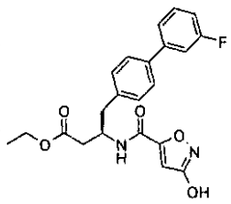
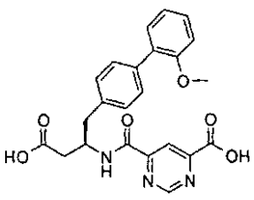
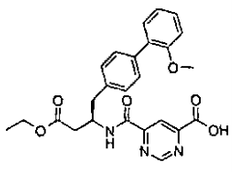
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 11-20	 ácido 4-[(R)-2-carboxi-1-(3'-cloro-bifenil-4-il-metil)-etil-carbamoil]-piridin-2-carboxílico		NaOH acuoso, EtOH, rt	1.03 minutos. (C)	439.2
Ejemplo 11-21	 ácido 2-[(R)-2-carboxi-1-(3'-cloro-bifenil-4-il-metil)-etil-carbamoil]-pirimidin-4-carboxílico		NaOH acuoso, EtOH, rt	0.89 minutos. (C)	440.1

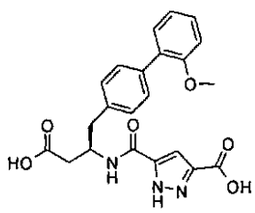
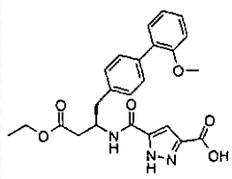
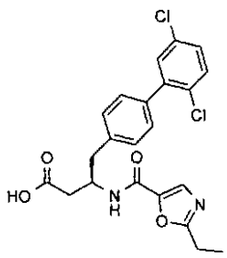
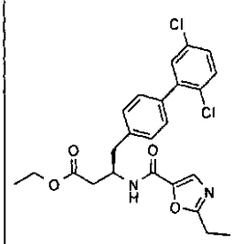
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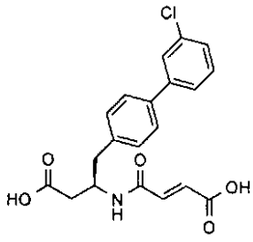
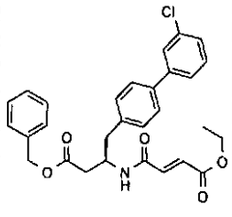
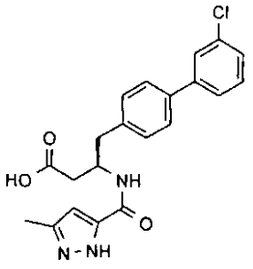
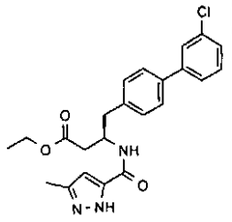
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 11-22	 ácido 5-[(R)-2-carboxi-1-(3'-cloro-bifenil-4-il-metil)-etil-carbamoil]-1H-pirrol-2-carboxílico		NaOH acuoso, EtOH, rt	1.09 minutos. (C)	427.3
Ejemplo 11-23	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-(oxalil-amino)-butírico		NaOH acuoso, EtOH, rt	0.9 minutos. (C)	362.1

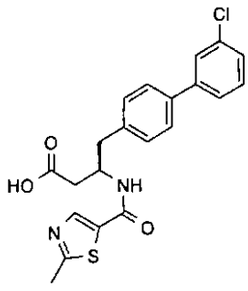
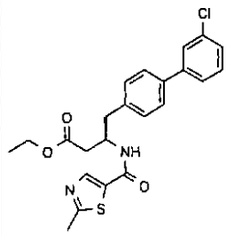
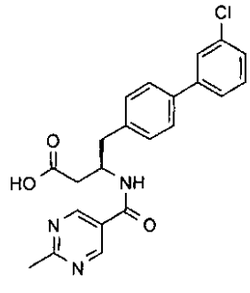
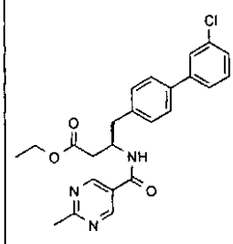
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 11-24	 ácido 5-[(R)-2-carboxi-1-(3'-fluoro-bifenil-4-il-metil)-etil-carbamoil]-1H-pirazol-3-carboxílico		NaOH acuoso, EtOH, 50°C	0.96 minutos. (C)	412.1
Ejemplo 11-25	 ácido 6-[(R)-2-carboxi-1-(3'-fluoro-bifenil-4-il-metil)-etil-carbamoil]-pirimidin-4-		NaOH acuoso, EtOH, rt	0.97 minutos. (C)	424.4

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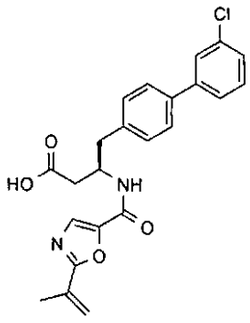
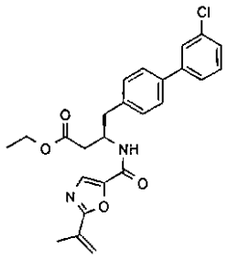
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	carboxílico				
Ejemplo 11-26	 ácido (R)-4-(3'-fluoro-bifenil-4-il)-3-[(3-hidroxi-isoxazol-5-carbonil)-amino]-butírico		NaOH acuoso, EtOH, rt	0.83 minutos. (C)	385.1
Ejemplo 11-27	 ácido 6-[(R)-2-carboxi-1-(2'-metoxi-bifenil-4-il-metil)-etil-carbamoil]-		NaOH acuoso, EtOH, rt	1.22 minutos. (C)	436.2

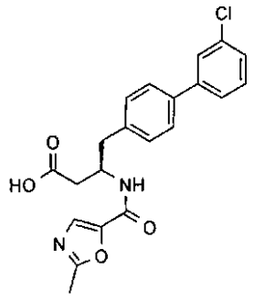
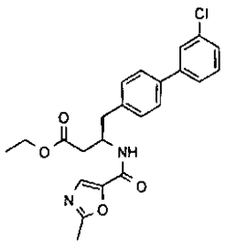
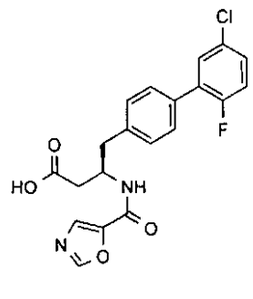
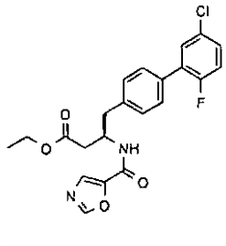
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	pirimidin-4-carboxílico				
Ejemplo 11-28	 ácido 5-[(R)-2-carboxi-1-(2'-metoxi-bifenil-4-il-metil)-etil-carbamoil]-1H-pirazol-3-carboxílico		NaOH acuoso, EtOH, 50°C	0.98 minutos. (C)	424.0
Ejemplo 11-29	 ácido (R)-4-(2',5'-dicloro-bifenil-4-		NaOH acuoso, MeOH, rt	1.52 minutos. (D)	448.1

Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	il)-3-[(2-etil-oxazol-5-carbonil)-amino]-butírico				
Ejemplo 11-30	 ácido (E)-3-[(R)-2-carboxi-1-(3'-cloro-bifenil-4-il-metil)-etil-carbamoil]-acrílico		NaOH acuoso, tetra-hidro-furano, MeOH, rt	1.12 minutos. (A)	388.3
Ejemplo 11-31	 ácido (R)-4-(3'-cloro-bifenil-4-il)-		NaOH acuoso, MeOH, rt	1.52 minutos. (D)	398.1

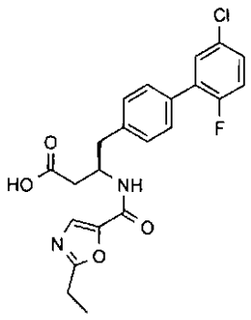
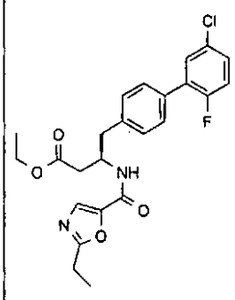
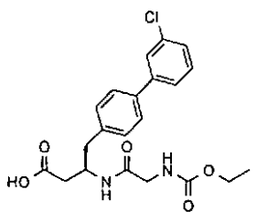
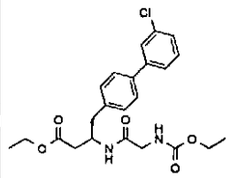
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	3-[(5-metil-2H-pirazol-3-carbonil)-amino]-butírico				
Ejemplo 11-32	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(2-metil-tiazol-5-carbonil)-amino]-butírico		NaOH acuoso, MeOH, rt	1.56 minutos. (D)	415.0
Ejemplo 11-33	 ácido (R)-4-(3'-		NaOH acuoso, MeOH, rt	1.56 minutos. (D)	410.1

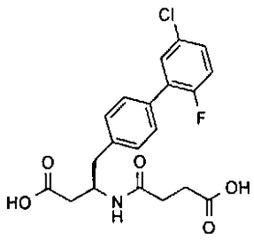
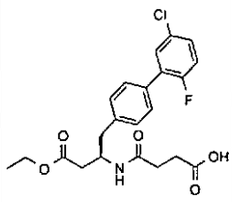
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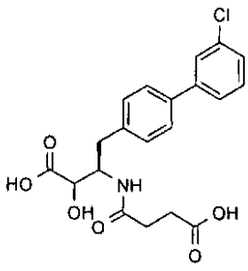
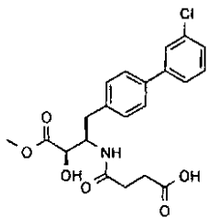
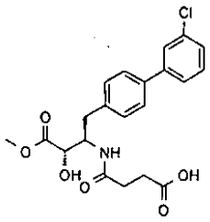
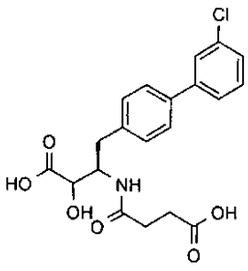
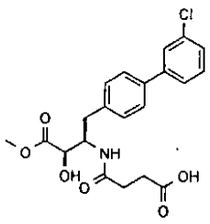
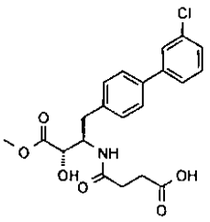
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	cloro-bifenil-4-il)-3-[(2-metil-pirimidin-5-carbonil)-amino]-butírico				
Ejemplo 11-34	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(2-isopropenil-oxazol-5-carbonil)-amino]-butírico		NaOH acuoso, MeOH, rt	1.75 minutos. (D)	425.1

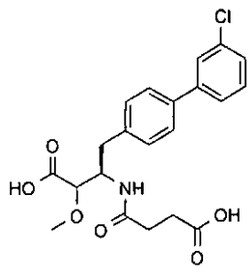
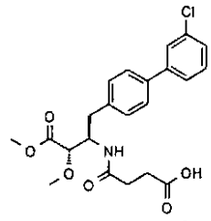
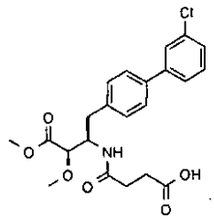
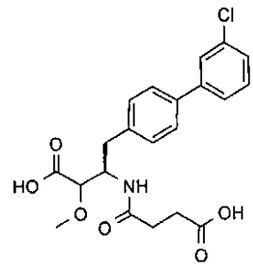
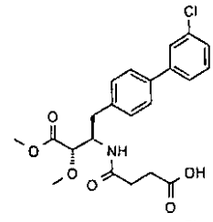
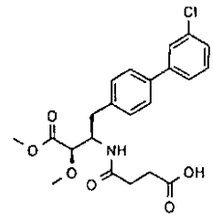
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 11-35	 ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(2-metil-oxazol-5-carbonil)-amino]-butírico		NaOH acuoso, MeOH, rt	1.63 minutos. (D)	399.1
Ejemplo 11-36	 ácido (R)-4-(5'-cloro-2'-fluoro-bifenil-4-il)-3-		NaOH acuoso, MeOH, rt	1.62 minutos. (D)	403.0

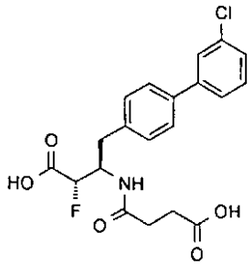
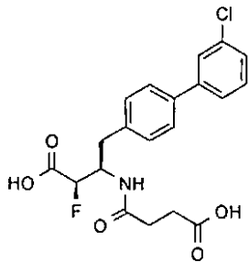
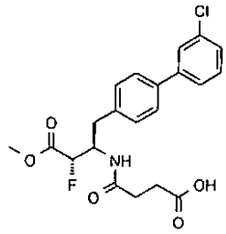
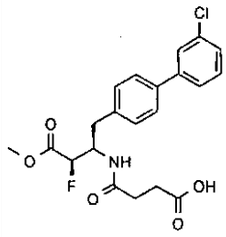
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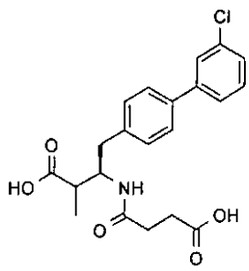
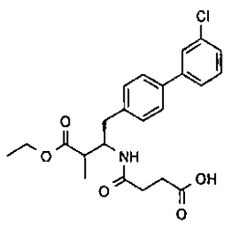
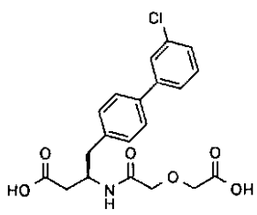
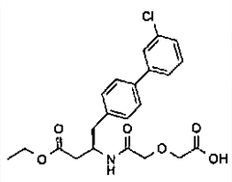
Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	[(oxazol-5-carbonil)-amino]-butírico				
Ejemplo 11-37	 ácido (R)-4-(5'-cloro-2'-fluoro-bifenil-4-il)-3-[(2-etil-oxazol-5-carbonil)-amino]-butírico		NaOH acuoso, MeOH, rt	1.73 minutos. (D)	431.1
Ejemplo 11-38			NaOH acuoso, tetra-hidro-	0.80 minutos. (B)	419.2

Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	ácido (R)-4-(3'-cloro-bifenil-4-il)-3-(2-etoxi-carbonil-amino-acetil-amino)-butírico		furano, MeOH, rt		
Ejemplo 11-39	 ácido (R)-3-(3-carboxi-propionil-amino)-4-(5'-cloro-2'-fluoro-bifenil-4-il)-butírico		NaOH acuoso, tetra-hidro-furano, MeOH, rt	0.66 minutos. (B)	408.1

Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 11-40	 (producto mayor) ácido (R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-hidroxi-butírico	 	NaOH acuoso, MeOH, rt	1.07 minutos. (A)	406.0
Ejemplo 11-41	 (producto menor) ácido (R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-	 	NaOH acuoso, MeOH, rt	1.04 minutos. (A)	406.0

Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	2-hidroxi-butírico				
Ejemplo 11-42	 (producto mayor) ácido (R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-metoxi-butírico	 	NaOH acuoso, MeOH, rt	0.97 minutos. (A)	420.1
Ejemplo 11-43	 (producto menor) ácido (R)-3-(3-carboxi-propionil-	 	NaOH acuoso, MeOH, rt	0.96 minutos. (A)	420.1

Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
	amino)-4-(3'-cloro-bifenil-4-il)-2-metoxi-butírico				
Ejemplo 11-44	  ácido (R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-fluoro-butírico	 	NaOH acuoso, MeOH, rt	1.07 min (A)	408.1

Ejemplo #	Producto	Material de partida	Condición de hidró-lisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 11-45	 ácido (R)-3-(3-carboxi-propionil-amino)-4-(3'-cloro-bifenil-4-il)-2-metil-butírico		NaOH acuoso, MeOH, rt	0.53 minutos. (B)	404
Ejemplo 11-46	 ácido (R)-3-(2-carboxi-metoxi-acetil-amino)-4-(3'-cloro-bifenil-4-il)-butírico		NaOH acuoso, MeOH, rt	0.37 minutos. (B)	406

Ejemplo 11-2: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.76 - 1.83 (m, 2 H) 2.15 - 2.21 (m, 4 H) 2.49 (A de ABX, J_{ab} = 15.7 Hz, J_{ax} = 7.3 Hz, 1 H) 2.53 (B de ABX, J_{ab} = 15.7 Hz, J_{bx} = 6.1 Hz, 1 H) 2.83 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.3 Hz, 1 H) 2.93 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 5.8 Hz, 1 H) 4.46 – 4.53 (m, 1 H) 7.30 – 7.33 (m, 3 H) 7.39 (t, J = 7.8 Hz, 1 H) 7.51 - 7.55 (m, 3 H) 7.59 – 7.60 (m, 1 H).

Ejemplo 11-3: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.77 - 1.84 (m, 2 H) 2.16 - 2.23 (m,4 H) 2.39 - 2.42 (m, 2 H) 2.49 (A de ABX, J_{ab} = 15.6 Hz, J_{ax} = 7.5 Hz, 1 H) 2.53 (B de ABX, J_{ab} = 15.6 Hz, J_{bx} = 6.1 Hz, 1 H) 2.83 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 6.1 Hz, 1 H) 2.91 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.3 Hz, 1 H) 3.75 (s, 3 H) 4.46 – 4.53 (m, 1 H) 6.97 - 7.04 (m, 2 H) 7.26 (d, J = 8.1 Hz, 2 H) 7.42 (d, J = 8.1 Hz, 2 H).

Ejemplo 11-4: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.77 - 1.84 (m, 2 H) 2.16 - 2.24 (m, 4 H) 2.49 (A de ABX, J_{ab} = 15.6 Hz, J_{ax} = 7.5 Hz, 1 H) 2.54 (B de ABX, J_{ab} = 15.6 Hz, J_{bx} = 6.1 Hz, 1 H) 2.83 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.2 Hz, 1 H) 2.91 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.1 Hz, 1 H) 3.77 (s, 3 H) 4.45 – 4.52 (m, 1 H) 7.03 (d, J = 8.6 Hz, 1 H) 7.24 – 7.28 (m, 3 H) 7.39 - 7.41 (m, 2 H).

Ejemplo 11-5: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.49 - 1.56 (m, 4 H) 2.13 (t, J = 6.8 Hz, 2 H) 2.23 (t, J = 6.9 Hz, 2 H) 2.45 - 2.56 (m, 2 H) 2.80 - 2.86 (m, 1 H) 2.91 - 2.96 (m, 1 H) 4.46 - 4.53 (m, 1 H) 7.31 - 7.33 (m, 3 H) 7.40 (t, J = 8.0 Hz, 1 H) 7.52 - 7.55 (m, 3 H) 7.59 (br t, J = 1.8 Hz, 1 H).

Ejemplo 11-6: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.39 - 2.57 (m, 4

H) 2.80 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 8.1 Hz, 1 H) 2.89 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.1 Hz, 1 H) 3.04 (t, J = 7.1 Hz, 2 H) 3.75 (s, 3 H) 4.40 – 4.47 (m, 1 H) 7.27 - 7.29 (m,2 H) 7.32 - 7.35 (m, 1 H) 7.41 (t, J = 7.8 Hz, 1 H) 7.51 - 7.54 (m, 3 H) 7.59 - 7.60 (m, 1 H) 7.83 - 7.84 (m, 1 H) 8.28 (br d, J = 7.1 Hz, 1 H) 8.55 (d, J = 5.6 Hz, 1 H) 8.62 (s, 1 H).

Ejemplo 11-7: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.47 (A de ABX, J_{ab} = 15.7 Hz, J_{ax} = 7.7 HZ, 1 H) 2.54 (B de ABX, J_{ab} = 15.7 Hz, Jbx = 5.8 Hz, 1 H) 2.64 - 2.75 (m, 2 H) 2.80 (A de ABX, J_{ab} = 13.7 Hz, J_{ax} = 8.3 Hz, 1 H) 2.92 (B de ABX, J_{ab} = 13.7 Hz, J_{bx} = 5.9 Hz, 1 H) 3.17 - 3.21 (m, 2 H) 4.43 – 4.50 (m, 1 H) 7.28 - 7.35 (m, 3 H) 7.39 - 7.43 (m, 1 H) 7.51 - 7.54 (m, 3 H) 7.59 (br t, J = 1.9 Hz, 1 H) 7.69 - 7.75 (m, 2 H) 8.29 - 8.32 (m, 1 H) 8.61 (d, J = 4.6 Hz, 1 H).

Ejemplo 11-8: ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.82 - 1.89 (m, 2 H) 2.29 (t, J = 7.3 Hz, 2 H) 2.56 (A de ABX, J_{ab} = 16.4 Hz, J_{ax} = 5.6 Hz, 1 H) 2.64 (B de ABX, J_{ab} = 16.4 Hz, J_{bx} = 5.1 Hz, 1 H) 2.95 (A de ABX, J_{ab} = 13.8 Hz, J_{ax} = 7.6 Hz, 1 H) 2.99 (B de ABX, J_{ab} = 13.8 Hz, J_{bx} = 7.2 Hz, 1 H) 3.30 (s, 3 H) 3.38 (t, J = 5.9 Hz, 2 H) 4.10 (q, J = 7.1 Hz, 2 H) 4.52 – 4.57 (m, 1 H) 6.59 (br d, J = 8.6 Hz, 1 H) 7.26 - 7.37 (m, 4 H) 7.42 - 7.45 (m, 1 H) 7.48 - 7.52 (m, 2 H) 7.55 (br t, J = 1.6 Hz, 1 H).

Ejemplo 11-9: ^{1}H RMN (400 MHz, CD_3CN+D_2O) δ ppm 2.43 - 2.56 (m, 2 H) 2.71 - 2.91 (m, 4 H) 3.21 - 3.34 (m, 2 H) 4.39 - 4.46 (m, 1 H) 7.27 (d, J = 8.3 Hz, 2 H) 7.34 - 7.49 (m, 7 H) 7.55 - 7.56 (m, 1 H) 7.65 - 7.70 (m, 2 H).

Ejemplo 11-10: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.38 - 2.41 (m, 2 H) 2.47 - 2.58 (m, 4 H) 2.85 – 2.90 (m, 1 H) 2.99 – 3.04 (m, 1 H) 4.48 – 4.55 (m, 1 H) 7.32 - 7.44 (m, 5 H) 7.53 - 7.56 (m, 1 H) 7.62 - 7.63 (m, 1 H).

Ejemplo 11-11: ^{1}H RMN (400 MHz, DMSO-d6): ^{1}H RMN (400 MHz, DMSO-d6): δ ppm 2.44-2.52 (m, 2H), 2.83-2.85 (d, J=6.82 Hz, 2H), 4.29-4.38 (m, 1H), 7.28-7.30 (d, J=8.34 Hz, 2H), 7.40-7.43 (t, J=7.83 Hz, 1H), 7.62-7.65 (m, 3H), 7.71-7.72 (t, J=1.77 Hz, 1H), 9.42-9.45 (M, 1H), 12.32 (s, 1H).

Ejemplo 11-12: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.54-2.59 (m, 1H), 2.64-2.70 (m, 1H), 2.88-2.93 (m, 1H), 2.98-3.03 (m, 1H), 4.56-4.63 (m, 1H), 7.30-7.32 (m, 2H), 7.37-7.40 (m, 1H), 7.43-7.47 (t, J=7.83 Hz, 1H), 7.59-7.61 (m, 3H), 7.67-7.68 (t, J=2.02 Hz, 1H), 8.32 (d, J=1.26 Hz, 1H), 9.17-9.19 (d, J=9.09 Hz, 1H), 9.50 (d, J=1.52 Hz, 1H), 12.34 (s, 1H), 14.14 (s, 1H).

Ejemplo 11-13: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.46-2.60 (m, 2H), 2.84-2.96 (m, 2H), 4.51 (m, 1H), 7.31 (d, J=8.34 Hz, 2H), 7.38-7.41 (m, 1H), 7.46 (t, 1H), 7.62 (d, J=8.34 Hz, 3H), 7.69 (t, 1H).

Ejemplo 11-14: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm) 2.75 - 2.99 (m, 1 H) 4.47 (d, J=7.58 Hz, 1 H) 6.49 (s, 1 H) 7.30 (d, J=8.34 Hz, 1 H) 7.37 - 7.43 (m, 1 H) 7.47 (t, J=7.83 Hz, 1 H) 7.63 (d, J=8.08 Hz, 2 H) 7.70 (t, J=1.77 Hz, 1 H) 8.80 (d, J=8.59 Hz, 1 H) 11.69 (s, 1 H) 12.04 - 12.58 (m, 1 H).

Ejemplo 11-15: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.81 - 2.96 (m, 2 H) 4.42 - 4.55 (m, 1 H) 7.31 (d, J=8.34 Hz, 2 H) 7.36 - 7.43 (m, 1

H) 7.47 (t, J=7.83 Hz, 1 H) 7.63 (d, J=8.34 Hz, 4 H) 7.69 (t, J=1.77 Hz, 1 H) 7.72 (s, 1 H) 8.54 (s, 1 H) 8.60 (d, J=8.59 Hz, 1 H) 12.29 (br. s., 1 H).

Ejemplo 11-16: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.53 - 2.64 (m, 2 H) 2.84 - 2.93 (m, 2 H) 4.41 - 4.59 (m, 1 H) 7.00 (d, J=2.02 Hz, 1 H) 7.31 (d, J=8.08 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.47 (t, J=7.83 Hz, 1 H) 7.58 - 7.65 (m, 3 H) 7.70 (t, J=1.77 Hz, 1 H) 8.72 (d, J=1.77 Hz, 1 H) 8.95 (d, J=8.59 Hz, 1 H) 12.31 (br. s., 1 H).

Ejemplo 11-17: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.46-2.60 (m, 2H), 2.83-2.98 (m, 2H), 4.52 (m, 1H), 6.61 (d, J=2.27 Hz, 1H), 7.31 (d, J=8.34 Hz, 2H), 7.37-7.42 (m, 1H), 7.46 (t, 1H), 7.62 (d, J=8.34 Hz, 3H), 7.69 (t, 1H), 7.74 (d, J=2.02 Hz, 1H), 8.13 (d, J=8.84 Hz, 1H).

Ejemplo 11-18: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.48-2.62 (m, 2H), 2.84-2.96 (m, 2H), 4.52 (m, 1H), 7.16 (d, J=3.54 Hz, 1H), 7.27 (d, J=3.79 Hz, 1H), 7.31 (d, J=8.34 Hz, 2H), 7.38-7.41 (m, 1H), 7.47 (t, 1H), 7.63 (d, J=8.34 Hz, 3H), 7.70 (t, 1H), 8.59 (d, J=8.59 Hz, 1H).

Ejemplo 11-19: ^{1}H RMN (400 MHz, DMSO-d6): ^{1}H RMN (400 MHz, DMSO-d6): δ ppm 2.54-2.67 (m, 2H), 2.88-2.92 (m, 1H), 2.99-3.05 (m, 1H), 4.53-4.62 (m, 1H), 7.31-7.33 (m, 2H), 7.37-7.39 (m, 1H), 7.43-7.47 (t, J = 7.58 Hz, 1H), 7.60-7.62 (m, 3H), 7.68 (m, 1H), 7.86-7.87 (d, J=4.55 Hz, 1H), 8.30 (s, 1H), 8.62-8.63 (d, J=4.80 Hz, 1H), 8.80-8.83 (d, J=9.09 Hz, 1H).

Ejemplo 11-20: ^{1}H RMN (400 MHz, DMSO-d6): ^{1}H RMN (400 MHz, DMSO-d6): δ ppm 2.50-2.53 (m, 1H), 2.56-2.59 (t, J=6.32 Hz,

1H), 2.90-2.98 (m, 2H), 4.51-4.58 (m, 1H), 7.33-7.35 (d, J=8.34 Hz, 2H), 7.39-7.42 (m, 1H), 7.45-7.49 (t, J=7.83 Hz, 1H), 7.61-7.65 (m, 3H), 7.69-7.70 (t, J=1.77 Hz, 1H), 7.90-7.91 (dd, J=1.77 Hz, 5.05 Hz, 1H), 8.38-8.39 (m, 1H), 8.83-8.85 (dd, J=0.76 Hz, 5.05 Hz, 1H), 8.91-8.93 (d, J=8.34 Hz, 1H).

Ejemplo 11-21: ^{1}H RMN (400 MHz, DMSO-d6): ^{1}H RMN (400 MHz, DMSO-d6): δ ppm 2.45-2.55 (m, 1H), 2.59-2.67 (m, 1H), 2.88-2.93 (m, 1H), 2.99-3.05 (m, 1H), 4.51-4.61 (m, 1H), 7.32-7.34 (d, J=8.08 Hz, 2H), 7.37-7.40 (m, 1H), 7.44-7.48 (t, J=7.58 Hz, 1H), 7.60-7.62 (t, J=7.83 Hz, 2H), 7.69 (s, 1H), 7.77 (s, 1H), 8.86-8.87 (d, J=4.04 Hz, 1H), 9.06 (s, 1H).

Ejemplo 11-22: ^{1}H RMN (400 MHz, DMSO-d6): δ ppm 2.49-2.53 (m, 2H), 2.90-2.92 (d, J=6.82 Hz, 2H), 4.42-4.51 (m, 1H), 6.72-6.73 (d, J=2.27 Hz, 2H), 7.32-7.34 (m, 2H), 7.39-7.42 (m, 1H), 7.45-7.49 (t, J = 7.83 Hz, 1H), 7.62-7.66 (m, 3H), 7.70-7.71 (t, J=1.77 Hz, 1H), 8.27-8.29 (d, J=8.08 Hz, 1H), 11.96 (s, 1H), 12.33 (s, 1H), 12.75 (s, 1H).

Ejemplo 11-23: ^{1}H RMN (400 MHz, DMSO-d6): ^{1}H RMN (400 MHz, DMSO-d6): δ ppm 2.44-2.55 (m, 2H), 2.79-2.89 (m, 2H), 4.29-4.38 (m, 1H), 7.27-7.29 (d, J=8.08 Hz, 2H), 7.39-7.42 (m, 1H), 7.45-7.49 (t, J=8.08 Hz, 1H), 7.62-7.64 (d, J=8.08 Hz, 3H), 7.70-7.71 (m, 1H), 8.85-8.87 (d, J=9.09 Hz, 1H), 12.30 (s, 1H).

Ejemplo 11-24: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.46-2.60 (m, 2H), 2.84-2.96 (m, 2H), 4.51 (m, 1H), 7.15 (m, 2H), 7.44-7.52 (m, 3H), 7.62 (d, J=8.34 Hz, 2H), 8.38 (d, amplia, J=7.58 Hz, 1H).

Ejemplo 11-25: ^{1}H RMN (400 MHz, DMSO-d6): δ ppm 2.54-2.59 (m,

1H), 2.64-2.70 (m, 1H), 2.88-2.93 (m, 1H), 2.98-3.03 (m, 1H), 4.56-4.65 (m, 1H), 7.13-7.18 (m, 1 H), 7.30-7.32 (d, J=8.34 Hz, 2H), 7.45-7.48 (m, 3H), 7.60-7.62 (d, J=8.34 Hz, 2H), 8.31-8.32 (d, J=1.26 Hz, 1H), 8.17-8.19 (d, J=9.09 Hz, 1H), 8.49 (d, J=1.26 Hz, 1H), 12.32 (s, 1H), 14.10 (s, 1H).

Ejemplo 11-26: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.52 - 2.62 (m, 2 H) 2.83 - 2.92 (m, 2 H) 4.47 (d, J=7.07 Hz, 1 H) 6.49 (s, 1 H) 7.11 - 7.21 (m, 1 H) 7.30 (d, J=8.34 Hz, 2 H) 7.42 - 7.55 (m, 3 H) 7.64 (d, J=8.34 Hz, 2 H) 8.80 (d, J=8.59 Hz, 1 H) 11.68 (br. s., 1 H) 12.30 (br. s., 1 H).

Ejemplo 11-27: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.51-2.57 (m, 1H), 2.64-2.70 (m, 1H), 2.84-2.89 (dd, J=6.06 Hz, 1H), 2.96-3.01 (dd, J=7.83 Hz, 1H), 3.72 (s, 3H), 4.54-4.63 (m, 1H), 6.96-7.00 (m, 1H), 7.06-7.08 (dd, J=0.76 Hz, 1H), 7.22-7.24 (m, 3H), 7.28-7.32 (m, 1H), 7.35-7.38 (m, 2H), 8.33-8.34 (d, J=1.26 Hz, 1H), 9.16-9.18 (d, J=9.09 Hz, 1H), 9.49 (d, J=1.52 Hz, 1H), 12.31 (s, 1H), 14.13 (s, 1H).

Ejemplo 11-28: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.52-2.60 (m, 2H), 2.73 (s, 1H), 2.89 (s, 1H), 2.81-2.95 (m, 2H), 3.74 (s, 3H), 4.50 (m, 1H), 7.00 (t, 1H), 7.08 (d, J=8.34 Hz, 1H), 7.15 (s, amplia, 1H), 7.23-7.26 (m, 3H), 7.29-7.33 (m, 1H), 7.38 (d, J=8.08 Hz, 2H), 8.39 (d, amplia, J=7.07 Hz, 1H).

Ejemplo 11-29: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.33 (t, *J*=7.6 Hz, 3 H) 2.66 (d, *J*=6.8 Hz, 2 H) 2.84 (q, *J*=7.6 Hz, 2 H) 2.98 (dd, *J*=13.6, 8.1 Hz, 1 H) 3.03 (dd, *J*=13.6, 6.6 Hz, 1 H) 4.64 - 4.76 (m, 1 H) 7.24 - 7.37 (m, 6 H) 7.40 - 7.45 (m, 1 H) 7.53 (s, 1 H).

Ejemplo 11-30: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.40 – 2.51 (m, 2 H) 2.79 – 2.90 (m, 2 H) 4.29 – 4.38 (m, 1 H) 6.47 (d, *J* = 15.7 Hz, 1 H) 6.88 (d, *J* = 15.7 Hz 1 H) 7.28 – 7.30 (m, 2 H) 7.39 – 7.41 (m, 1 H) 7.47 (t, *J* = 8.0 Hz, 1 H) 7.62 – 7.65 (m, 2 H) 7.70 – 7.71 (m, 1 H) 8.54 (d, *J* = 8.1 Hz, 1 H) 7.31 (d, *J* = 8.3 HZ, 2 H) 7.40 – 7.43 (m, 1 H) 7.47 – 7.50 (m, 1 H) 7.62 – 7.65 (m, 3 H) 7.69 – 7.71 (m, 1 H) 8.54 (d, J = 8.1 Hz, 1 H)

Ejemplo 11-31: ^{1}H RMN (400 MHz, DMSO-d_6) δppm 2.22 (s, 3 H) 2.43 - 2.49 (m, 1 H) 2.52 - 2.60 (m, 1 H) 2.84 (dd, *J*=13.6, 6.1 Hz, 1 H) 2.94 (dd, *J*=13.6, 8.1 Hz, 1 H) 4.39 - 4.58 (m, 1 H) 6.33 (s, 1 H) 7.30 (d, *J*=8.3 Hz, 2 H) 7.36 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.61 (d, *J*=8.3 Hz, 3 H) 7.69 (t, *J*=1.9 Hz, 1 H) 8.02 (d, *J*=7.8 Hz, 1 H).

Ejemplo 11-32: ^{1}H RMN (400 MHz, DMSO-d_6) δppm 2.51 - 2.56 (m, 2 H) 2.89 (d, *J*=6.8 Hz, 2 H) 3.31 (s, 3 H) 4.33 - 4.57 (m, 1 H) 7.31 (d, *J*=8.1 Hz, 2 H) 7.37 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.60 - 7.66 (m, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 8.15 (s, 1 H) 8.50 (d, *J*=8.3 Hz, 1 H) 12.24 (br. s., 1 H).

Ejemplo 11-33: ^{1}H RMN (400 MHz, DMSO-d_6) δppm 2.52 - 2.60 (m, 2 H) 2.66 (s, 3 H) 2.93 (d, *J*=6.8 Hz, 2 H) 4.43 - 4.63 (m, 1 H) 7.33 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.42 (m, 1 H) 7.46 (t, *J*=7.8 Hz, 1 H) 7.58 - 7.66 (m, 3 H) 7.69 (t, *J*=1.8 Hz, 1 H) 8.74 (d, *J*=8.3 Hz, 1 H) 8.98 (s, 2 H) 12.28 (br. s., 1 H).

Ejemplo 11-34: ^{1}H RMN (400 MHz, MeOD) δppm 2.15 (s, 3 H) 2.67 (d, *J*=6.6 Hz, 2 H) 2.98 (dd, *J*=13.9, 8.3 Hz, 1 H) 3.03 (dd, *J*=14.1,

6.8 Hz, 1 H) 4.62 - 4.77 (m, 1 H) 5.57 (s, 1 H) 6.16 (s, 1 H) 7.27 - 7.32 (m, 1 H) 7.32 - 7.41 (m, 3 H) 7.46 - 7.54 (m, 3 H) 7.56 (t, *J*=1.8 Hz, 1 H) 7.65 (s, 1 H) 8.55 (d, *J*=8.6 Hz, 1 H).

Ejemplo 11-35: ^{1}H RMN (400 MHz, CD_3OD) δppm 2.42 (s, 3 H) 2.63 (d, *J*=6.3 Hz, 2 H) 2.99 (d, *J*=7.1 Hz, 2 H) 4.59 - 4.73 (m, 1 H) 7.25 - 7.30 (m, 1 H) 7.30 - 7.37 (m, 3 H) 7.41 - 7.50 (m, 3 H) 7.53 (t, *J*=1.8 Hz, 1 H) 8.15 (s, 1 H).

Ejemplo 11-36: ^{1}H RMN (400 MHz, DMSO-d_6) δppm 2.51 - 2.61 (m, 2 H) 2.87 (dd, *J*=13.1, 5.6 Hz, 1 H) 2.94 (dd, *J*=13.4, 7.6 Hz, 1 H) 4.41 - 4.60 (m, 1 H) 7.29 - 7.38 (m, 3 H) 7.45 (ddd, *J*=8.7, 4.2, 2.8 Hz, 1 H) 7.49 (d, *J*=6.8 Hz, 2 H) 7.56 (dd, *J*=6.8, 2.5 Hz, 1 H) 7.71 (s, 1 H) 8.53 (s, 1 H) 8.59 (d, *J*=8.6 Hz, 1 H) 12.26 (br. s., 1 H).

Ejemplo 11-37: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.32 (t, J=7.6 Hz, 3 H) 2.66 (d, J=6.8 Hz, 2 H) 2.83 (q, J=7.6 Hz, 2 H) 2.98 (dd, J=13.6, 7.8 Hz, 1 H) 3.03 (dd, J=14.7, 6.8 Hz, 1 H) 4.61 - 4.80 (m, 1 H) 7.13 (dd, J=18.9, 10.1 Hz, 1 H) 7.25 - 7.32 (m, 1 H) 7.32 - 7.37 (m, 2 H) 7.37 - 7.45 (m, 3 H) 7.54 (s, 1 H).

Ejemplo 11-38: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1.15 (t, *J* = 7.73 Hz, 3 H) 2.39 (d, *J* = 6.8 Hz, 2 H) 2.79 (d, *J* = 6.8 Hz, 2 H) 3.46 – 3.56 (m, 2 H) 3.91 – 4.01 (m, 2 H) 4.21 – 4.29 (m, 1 H) 7.14 – 7.17 (m, 1 H) 7.28 (d, *J* = 8.3 Hz, 2 H) 7.39 – 7.42 (m, 1 H) 7.48 (t, *J* = 7.83 Hz, 1 H) 7.61 – 7.64 (m, 3 H) 7.69 – 7.70 (m, 1 H) 7.84 (d, *J* = 8.4 Hz, 1 H) 12.23 (br s, 1 H).

Ejemplo 11-39: ^{1}H RMN (400 MHz, Metanol-d4) δ ppm 2.39 – 2.56 (m, 6 H) 2.87 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.6 Hz, 1 H) 2.94 (B de

ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.1 Hz, 1 H) 4.43 – 4.50 (m, 1 H) 7.15 – 7.20 (m, 1 H) 7.31 – 7.35 (m, 3 H) 7.45 – 7.48 (m, 3 H).

Ejemplo 11-40: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.24-2.37 (m, 4H), 2.73 (dd, 1H, J = 7.83, 13.4 Hz), 2.88 (dd, 1H, J = 7.33, 13.4 Hz), 3.93 (s, 1H), 4.26-4.36 (m, 1H), 5.35 (bs, 1H), 7.33 (d, 2H, J = 8.08 Hz), 7.38-7.43 (m, 1H), 7.48 (t, 1H, J = 7.83 Hz), 7.63 (d, 3H, J = 8.34 Hz), 7.70 (t, 1H, J = 2.02 Hz), 7.73 (d, 1H, J = 9.09 Hz), 12.26 (bs, 2H).

Ejemplo 11-41: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.21-2.33 (m, 4H), 2.65-2.81 (m, 2H), 4.02 (d, 1H, J = 4.04 Hz), 4.24-4.32 (m, 1H), 5.56 (bs, 1H), 7.27 (d, 2H, J = 8.34 Hz), 7.37-7.42 (m, 1H), 7.47 (t, 1H, J = 7.83 Hz), 7.58 (d, 2H, J = 8.34 Hz), 7.60-7.64 (m, 1H), 7.69 (t, 1H, J = 1.77 Hz), 7.96 (d, 1H, J = 8.84 Hz), 12.03 (bs, 1H), 12.60 (bs, 1H).

Ejemplo 11-42: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.22-2.37 (m, 4H), 2,74 (dd, 1H, J = 8.34, 13.4 Hz), 2.86 (dd, 1H, J = 6.82, 13.4 Hz), 3.34 (s, 3H), 3.62 (d, 1H, J = 2.78 Hz), 4.34-4.44 (m, 1H), 7.31 (d, 2H, J = 8.34 Hz), 7.38-7.43 (m, 1H), 7.48 (t, 1H, J = 7.83 Hz), 7.63 (d, 3H, J = 8.34 Hz), 7.71 (s, 1H), 7.89 (d, 1H, J = 9.35 Hz).

Ejemplo 11-43: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.17-2.37 (m, 4H), 2.64-2.81 (m, 2H), 3.37 (s, 3H), 3.77 (d, 1H, J = 4.04 Hz), 4.25-4.34 (m, 1H), 7.25 (d, 2H, J = 8.08 Hz), 7.38-7.42 (m, 1H), 7.47 (t, 1H, J = 7.83 Hz), 7.56-7.64 (m, 3H), 7.68 (t, 1H, J = 1.77 Hz), 8.05 (d, 1H, J = 8.84 Hz), 12.05 (bs, 1H), 12.89 (bs, 1H).

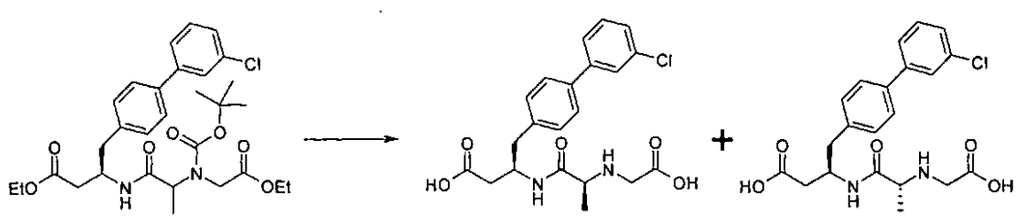
Ejemplo 11-44: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.20-2.39 (m,

4H), 2.65-2.87 (m, 2H), 4.37-4.56 (m, 1H), 4.91 (d, 0.5 horas, J = 2.78 Hz), 5.04 (d, 0.5 horas, J = 3.03 Hz), 7.29 (d, 2H, J = 8.34 Hz), 7.38-7.43 (m, 1H), 7.47 (t, 1H, J = 7.83 Hz), 7.58-7.65 (m, 3H), 7.69 (t, 1H, J = 1.77 Hz), 8.27 (d, 1H, J = 8.59 Hz), 12.05 (bs, 1H), 13.57 (bs, 1H).

Ejemplo 11-45: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1.10 (d, *J*=7.1 Hz, 3 H), 2.17 - 2.37 (m, 4 H), 2.57 - 2.78 (m, 3 H), 4.19 - 4.31 (m, *J*=9.2, 9.2, 4.5, 4.3 Hz, 1 H), 7.30 (d, *J*=8.1 Hz, 2 H), 7.37 - 7.42 (m, 1 H), 7.47 (t, *J*=7.8 Hz, 1 H), 7.57 - 7.65 (m, 3 H), 7.70 (t, *J*=1.8 Hz, 1 H), 7.86 (d, *J*=8.8 Hz, 1 H), 12.21 (br. s., 2 H).

Ejemplo 11-46: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.45 (dd, *J*=6.6, 3.5 Hz, 1 H), 2.82 (d, *J*=7.1 Hz, 1 H), 3.88 (dd, *J*=20.2, 15.2 Hz, 1 H), 4.03 (s, 1 H), 4.29 - 4.41 (m, 1 H), 7.29 (d, *J*=8.3 Hz, 1 H), 7.37 - 7.43 (m, 1 H), 7.48 (t, *J*=8.0 Hz, 1 H), 7.62 (d, *J*=8.3 Hz, 2 H), 7.70 (t, *J*=1.8 Hz, 1 H), 7.89 (d, *J*=8.8 Hz, 1 H), 11.65 - 13.45 (m, 1 H).

Ejemplo 11-47 / 48: Ácido (R)-3-[(S)-2-(carboxi-metil-amino)-propionil-amino]-4-(3'-cloro-bifenil-4-il)-butírico y ácido (R)-3-[(R)-2-(carboxi-metil-amino)-propionil-amino]-4-(3'-cloro-bifenil-4-il)-butírico



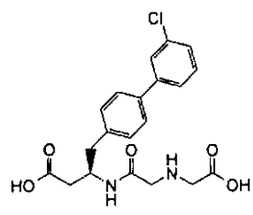
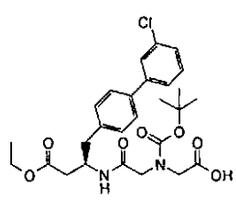
A una solución de etil-éster del ácido (R)-3-[2-(terbutoxi-

carbonil-etoxi-carbonil-metil-amino)-propionil-amino]-4-(3'-cloro-bifenil-4-il)-butírico (290 miligramos, 0.504 milimoles) en tetra-hidrofurano (3 mililitros) y metanol (0.5 mililitros) a temperatura ambiente, se le agrega NaOH 2M (1.009 mililitros, 2.017 milimoles). La reacción se agita a temperatura ambiente durante la noche. La mezcla se concentra a sequedad y el producto crudo se absorbe en dicloro-metano (3.00 mililitros), a lo cual se agrega ácido trifluoro-acético (3.89 mililitros, 50.4 milimoles), y la mezcla se agita a temperatura ambiente durante 2 horas. La reacción se concentra para la purificación mediante HPLC. HPLC en fase inversa [del 25 al 50 por ciento de ACN-H_2O (ácido trifluoro-acético al 0.1 por ciento) durante 10 minutos mediante una columna Sunfire C18], para dar el ácido (R)-3-[(S)-2-(carboxi-metil-amino)-propionil-amino]-4-(3'-cloro-bifenil-4-il)-butírico y el ácido (R)-3-[(R)-2-(carboxi-metil-amino)-propionil-amino]-4-(3'-cloro-bifenil-4-il)-butírico.

Ácido (R)-3-[(S)-2-(carboxi-metil-amino)-propionil-amino]-4-(3'-cloro-bifenil-4-il)-butírico: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.28 (d, *J*=7.1 Hz, 3 H), 2.40 (dd, *J*=15.7, 8.3 Hz, 1 H), 2.51 - 2.56 (m, 1 H), 2.76 (dd, *J*=13.4, 8.1 Hz, 1 H), 2.87 (dd, *J*=13.4, 5.3 Hz, 1 H), 3.43 - 3.52 (m, 3 H), 3.67 (q, *J*=6.7 Hz, 1 H), 4.25 - 4.36 (m, 1 H), 7.30 (d, *J*=8.3 Hz, 2 H), 7.38 - 7.43 (m, 1 H), 7.48 (t, *J*=7.8 Hz, 1 H), 7.59 - 7.65 (m, 3 H), 7.70 (t, *J*=1.8 Hz, 1 H), 8.41 (d, *J*=8.3 Hz, 1 H). HRMS: Calculado para $C_{21}H_{23}ClN_2O_5$: 418.1295; encontrado: m/z 418.1307. LCMS (condición A): 419 (M+1); tiempo de retención = 0.93 minutos; ácido (R)-3-[(R)-2-(carboxi-metil-amino)-propionil-

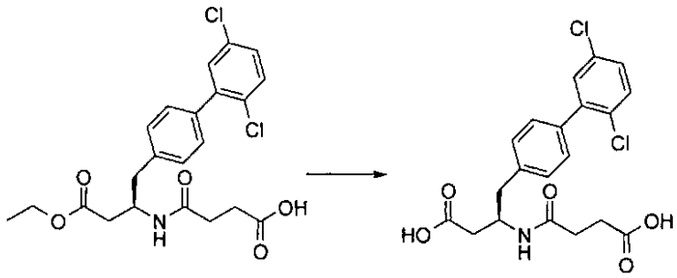
amino]-4-(3'-cloro-bifenil-4-il)-butírico: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.17 (d, *J*=6.8 Hz, 3 H), 2.41 - 2.49 (m, 0 H), 2.51 - 2.57 (m, 1 H), 2.73 (dd, *J*=13.4, 9.1 Hz, 1 H), 2.91 (dd, *J*=13.4, 4.8 Hz, 1 H), 3.55 - 3.67 (m, 2 H), 3.67 - 3.74 (m, 1 H), 4.26 - 4.40 (m, 1 H), 7.29 (d, *J*=8.3 Hz, 2 H), 7.39 - 7.44 (m, 0 H), 7.48 (t, *J*=7.8 Hz, 0 H), 7.59 - 7.65 (m, 3 H), 7.69 (t, *J*=1.8 Hz, 1 H), 8.43 (d, *J*=8.6 Hz, 1 H). HRMS: Calculado para $C_{21}H_{23}ClN_2O_5$: 418.1295; encontrado: m/z 418.1305. LCMS (condición A): 419 (M+1); tiempo de retención = 0.99 minutos.

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 11-47/48:

Ejemplo #	Producto	Material de partida	HPLC-RT (condición)	MS (M+1)
Ejemplo 11-49	 ácido (R)-3-[2-(carboxi-metil-amino)-acetil-amino]-4-(3'-cloro-bifenil-4-il)-butírico		1.12 minutos. (A)	405.2

Ejemplo 11-49: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.39 – 2.50 (m, 2 H) 2.77 – 2.89 (m, 2 H) 3.61 – 3.71 (m, 2 H) 3.81 (s, 2 H) 4.26 – 4.35 (m, 1 H) 7.31 (d, *J* = 8.3 HZ, 2 H) 7.40 – 7.43 (m, 1 H) 7.47 – 7.50 (m, 1 H) 7.62 – 7.65 (m, 3 H) 7.69 – 7.70 (m, 1 H) 8.49 (d, *J* = 7.3 Hz, 1 H).

Ejemplo 12-1: Síntesis de ácido (R)-4-(1-carboxi-3-(3'-cloro-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico

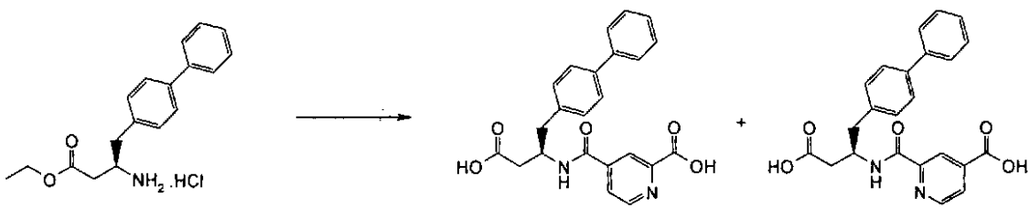


A una solución del ácido (R)-4-(1-(2',5'-dicloro-bifenil-4-il)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico (106 miligramos, 0.234 milimoles) en tetrahidrofurano (2 mililitros) y metanol (0.1 mililitros), se le agrega una solución acuosa de NaOH 1M (1.406 mililitros, 1.406 milimoles) a temperatura ambiente. Después de agitar durante 4.5 horas, la reacción se apaga con HCl acuoso 0.1 M (3 mililitros), y los productos se extraen con EtOAc. La capa orgánica combinada se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida. El producto crudo se tritura en dicloro-metano. El precipitado se recolecta en un embudo, se lava con dicloro-metano, y se seca bajo presión reducida, para dar el ácido (R)-4-(1-carboxi-3-(3'-cloro-bifenil-4-il)-propan-2-il-amino)-4-oxo-butanoico (64.0 miligramos) como un sólido blanco; HPLC - tiempo de retención

= 1.24 minutos (condición A); MS (m+1) = 424.07; ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.38-2.42 (m, 2 H) 2.45 - 2.57 (m, 4 H) 2.87 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 7.6 Hz, 1 H) 2.95 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 6.1 Hz, 1 H) 4.44 - 4.51 (m, 1 H) 7.30 - 7.37 (m, 6 H) 7.47 (d, J = 8.4 Hz, 1 H).

Ejemplo 13-1: Síntesis de ácido (R)-4-(1-(bifenil-4-il)-3-carboxi-propan-2-il-carbamoil)-picolínico

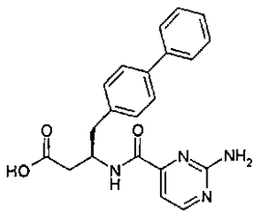
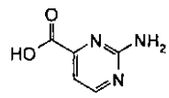
Ejemplo 13-2: Síntesis de ácido (R)-2-(1-(bifenil-4-il)-3-carboxi-propan-2-il-carbamoil)-isonicotínico



A una solución del clorhidrato de 3-amino-4-(bifenil-4-il)-butanoato de (R)-etilo (200 miligramos, 0.625 milimoles), hidrato de ácido 2,4-piridin-dicarboxílico (151 miligramos, 0.813 milimoles), EDCI (132 miligramos, 0.688 milimoles), y 1-hidroxi-7-aza-benzotriazol (94 miligramos, 0.688 milimoles) en N,N-dimetil-formamida (6 mililitros), se le agrega di-isopropil-etil-amina (0.164 mililitros, 0.938 milimoles). La mezcla de reacción se deja agitándose durante 3 horas. Entonces, la mezcla de reacción se diluye con H_2O. El sólido precipitado se recolecta en un embudo y se seca bajo presión reducida. A una solución del producto crudo en tetra-hidrofurano (8 mililitros) y metanol (1 mililitro), se le agrega NaOH 1M acuoso (2.5 mililitros, 2.5 milimoles). Después de agitar durante 1

hora, la reacción se apaga con ácido cítrico al 5 por ciento y salmuera, y los productos se extraen con EtOAc. La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra. El residuo resultante se purifica mediante HPLC de preparación utilizando un gradiente del 20 por ciento de MeCN/agua (ácido trifluoro-acético al 0.1 por ciento) al 100 por ciento de MeCN, para dar el ácido (R)-4-(1-(bifenil-4-il)-3-carboxi-propan-2-il-carbamoil)-picolínico y el ácido (R)-2-(1-(bifenil-4-il)-3-carboxi-propan-2-il-carbamoil)-isonicotínico como sólidos blancos, respectivamente (Ejemplo 13-1: 33 miligramos; Ejemplo 13-2: 36 miligramos). Ejemplo 13-1, HPLC - tiempo de retención = 1.50 minutos (condición D); MS (m+1) = 405.1; ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.53 - 2.62 (m, 2 H) 2.88 - 2.97 (m, 2 H) 4.50 - 4.59 (m, 1 H) 7.31 - 7.35 (m, 3 H) 7.42 - 7.45 (m, 2 H) 7.57 - 7.64 (m, 4 H) 7.89 (dd, J = 5, 1.6 Hz, 1 H) 8.83 (dd, J = 5, 0.8 Hz, 1 H) 8.37 (dd, J = 1.6, 0.8 Hz) 8.89 (d, J = 8.3 Hz, 1 H). Ejemplo 13-2, HPLC - tiempo de retención = 1.24 minutos (condición A); MS (m+1) = 405.1; ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.52 - 2.68 (m, 2 H) 2.91 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 6.1 Hz, 1 H) 3.01 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 8.1 Hz, 1 H) 4.56 - 4.65 (m, 1 H) 7.29 - 7.34 (m, 3 H) 7.41 - 7.45 (m, 2 H) 7.55 - 7.64 (m, 4 H) 7.99 (dd, J = 5, 1.6 Hz, 1 H) 8.34 (dd, J = 1.6, 0.8 Hz, 1 H) 8.84 (dd, J = 5, 0.8 Hz, 1 H) 8.90 (d, J = 9.1 Hz, 1 H) 12.26 (br s, 1 H) 13.87 (br s, 1 H).

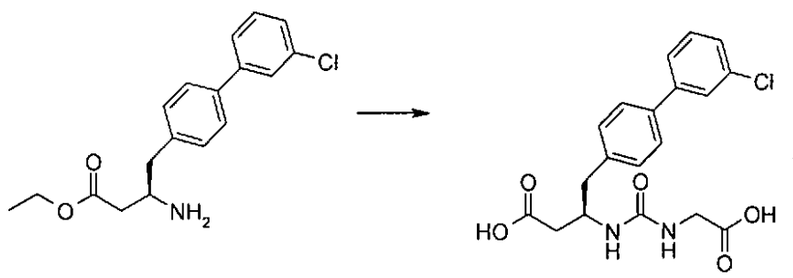
Se preparan los siguientes compuestos empleando un procedimiento similar al descrito en los Ejemplos 13-1 y 13-2:

Ejemplo #	Producto	Condición	HPLC-RT (condición)	MS (M+1)
Ejemplo 13-3	 ácido (R)-3-(2-amino-pirimidin-4-carboxamido)-4-(bifenil-4-il)-butanoico	 PyBOP, DIPEA, N,N-dimetil-formamida, RT; NaOH acuoso, tetrahidro-furano, MeOH, RT	1.37 minutos. (A)	377.0

Ejemplo 13-3: ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 2.55 (d, J = 6.6 Hz, 2 H) 2.91 (A de ABX, J_{ab} = 13.6 Hz, J_{ax} = 6.3 Hz, 1 H) 2.96 (B de ABX, J_{ab} = 13.6 Hz, J_{bx} = 7.6 Hz, 1 H) 4.46 - 4.55 (m, 1 H) 6.86 (br s, 2 H) 7.02 (d, J = 4.8 Hz, 1 H) 7.28 - 7.36 (m, 3 H) 7.42 - 7.46 (m, 2 H) 7.58 - 7.65 (m, 4 H) 8.39 (d, J = 9.1 Hz, 1 H) 8.45 (d, J = 4.8 Hz, 1 H).

Ejemplo 14-1: Síntesis de ácido (R)-3-(3-carboxi-metil-ureido)-4-(3'-cloro-bifenil-4-il)-butírico

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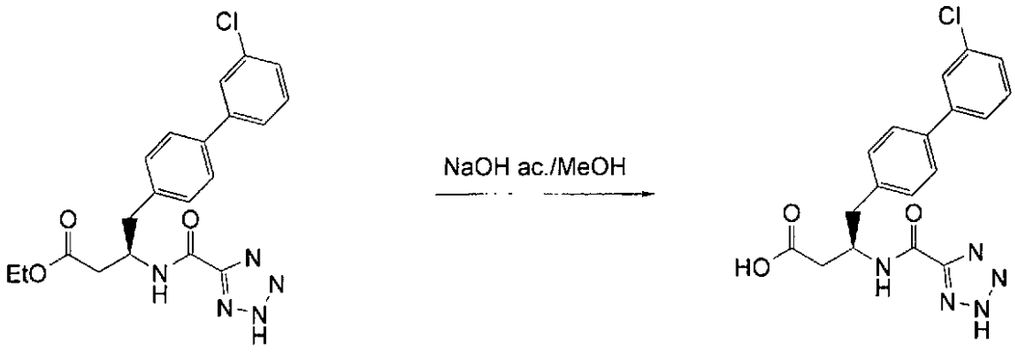


A una solución del intermediario 16-1 (90 miligramos, 0.254 milimoles), y acetato de isocianato de etilo (39.4 miligramos, 0.305 milimoles) en N,N-dimetil-formamida (3 mililitros), se le agrega piridina (2.93 gramos, 37.1 milimoles), y la mezcla se agita a temperatura ambiente durante 2 horas. El solvente se remueve bajo presión reducida, y el residuo se utiliza directamente en el siguiente paso.

En seguida, el residuo anterior se disuelve en EtOH (1 mililitro), y se agrega NaOH 1N (3 mililitros, 3 milimoles). La mezcla se agita a temperatura ambiente durante 2 horas, entonces se acidifica con HCl 1N. La mezcla se extrae con EtOAc, y la fase orgánica se lava con agua, salmuera, entonces se seca sobre sulfato de sodio. El solvente se remueve bajo presión reducida, y el residuo se purifica mediante HPLC de preparación utilizando un gradiente desde el 10 por ciento de MeCN/agua hasta el 100 por ciento de MeCN (+ ácido trifluoro-acético al 0.1 por ciento). La liofilización de las fracciones apropiadas da el compuesto del título; HPLC - tiempo de retención de 0.98 minutos (condición C); MS 391.3 (M+1); ^{1}H RMN (400 MHz, DMSO-d6): δ ppm 2.34 (d, J=7.33 Hz, 2H), 2.79 (d, J=6.57 Hz, 2H), 3.67 (d, J=5.56 Hz, 2H), 4.04-4.12 (m, 1H), 6.15 (t, J=5.81

Hz, 1H), 6.23 (d, J=8.34 Hz, 1H), 7.28-7.30 (m, 2H), 7.39-7.42 (m, 1H), 7.48 (t, J = 7.83 Hz, 1H), 7.62-7.65 (m, 3H), 7.71 (t, J=1.77 Hz, 1H), 12.32 (s, br, 2H).

Ejemplo 15-1: Ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(2H-tetrazol-5-carbonil)-amino]-butírico

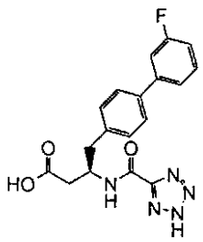
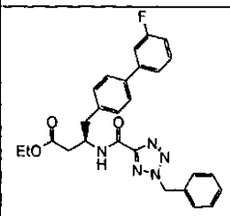
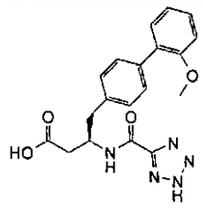
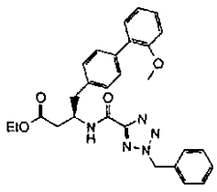


A una suspensión del material de partida en metanol (5 mililitros) a temperatura ambiente, se le agrega NaOH (2 mililitros, 6.00 milimoles), y la mezcla se agita hasta que la reacción esté completa. La mezcla de reacción se acidifica a un pH <4 y se purifica mediante HPLC (del 15 por ciento al 60 por ciento de acetonitrilo-H_2O con ácido trifluoro-acético al 0.1 por ciento), para dar el ácido (R)-4-(3'-cloro-bifenil-4-il)-3-[(2H-tetrazol-5-carbonil)-amino]-butírico (80 miligramos).

HPLC - tiempo de retención = 0.95 minutos (condición B); MS (m+1) = 386.1; ^{1}H RMN (400 MHz, DMSO-d_6) d ppm 2.52 - 2.61 (m, 1 H), 2.61 - 2.72 (m, 1 H), 2.84 - 2.99 (m, 2 H), 4.51 - 4.64 (m, 1 H), 7.31 (d, J=8.1 Hz, 2 H), 7.36 - 7.41 (m, 1 H), 7.46 (t, J=7.8 Hz, 1 H), 7.61 (d, J=8.3 Hz, 3 H), 7.68 (t, J=1.9 Hz, 1 H), 9.31 (d, J=8.8 Hz, 1

H), 12.32 (br. s., 1 H).

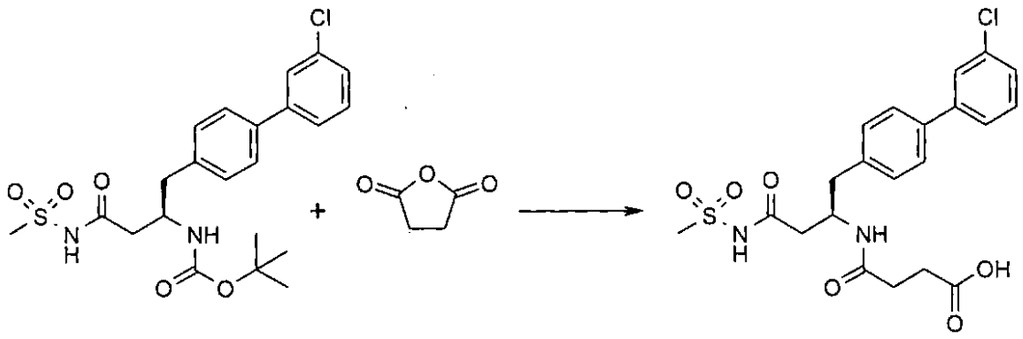
Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 15-1:

Ejemplo #	Producto	Material de partida y condición de hidrólisis	HPLC-RT (condición)	MS (M+1)
Ejemplo 15-2	 ácido (R)-4-(3'-fluoro-bifenil-4-il)-3-[(2H-tetrazol-5-carbonil)-amino]-butírico	 1 atm. H_2, Pd/C, EtOH, RT; Seguido por NaOH acuoso y EtOH	1.26 minutos. (A)	370.2
Ejemplo 15-3	 ácido (R)-4-(2'-metoxi-bifenil-4-il)-3-[(2H-tetrazol-5-carbonil)-amino]-butírico	 1 atm. H_2, Pd/C, EtOH, RT; Seguido por NaOH acuoso y EtOH	1.24 minutos. (A)	382.2

Ejemplo 15-2: ^{1}H RMN (400 MHz, DMSO-d_6) d ppm 2.52 - 2.72 (m, 2 H), 2.86 - 3.00 (m, 2 H), 4.52 - 4.65 (m, 1 H), 7.11 - 7.20 (m, 1 H), 7.31 (d, J=8.1 Hz, 2 H), 7.43 - 7.51 (m, 3 H), 7.61 (d, J=8.3 Hz, 2 H), 9.28 (d, J=8.8 Hz, 1 H), 12.29 (br. s., 1 H).

Ejemplo 15-3: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.52 - 2.60 (m, J=15.9, 5.8 Hz, 1 H), 2.67 (dd, J=15.9, 7.8 Hz, 1 H), 2.87 (dd, J=13.6, 5.8 Hz, 1 H), 2.95 (dd, J=13.6, 8.3 Hz, 1 H), 3.73 (s, 3 H), 4.52 - 4.64 (m, 1 H), 7.00 (td, J=7.4, 1.1 Hz, 1 H), 7.08 (d, J=9.1 Hz, 1 H), 7.22 - 7.27 (m, 3 H), 7.28 - 7.34 (m, 1 H), 7.37 (d, J=8.3 Hz, 2 H), 9.30 (d, J=8.8 Hz, 1 H), 12.28 (br. s., 1 H).

Ejemplo 16-1: Ácido N-[(R)-1-(3'-cloro-bifenil-4-il-metil)-3-metan-sulfonil-amino-3-oxo-propil]-succinámico

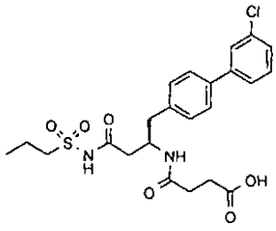
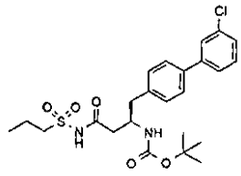


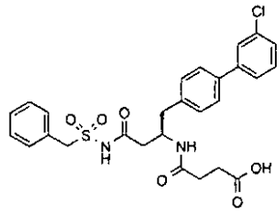
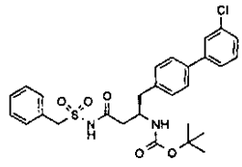
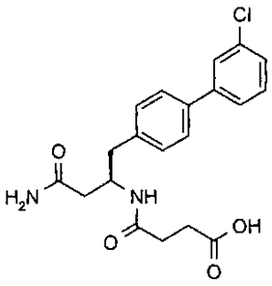
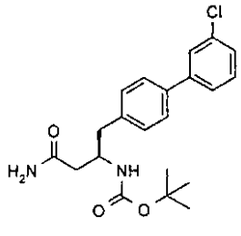
El terbutil-éster del ácido [(R)-1-(3'-cloro-bifenil-4-il-metil)-3-metan-sulfonil-amino-3-oxo-propil]-carbámico (150 miligramos, 0.321 milimoles), se trata con HCl 4M en dioxano. Después de agitarse a temperatura ambiente durante 1 hora, la mezcla de reacción se concentra al vacío. A este residuo en dicloro-metano (2 mililitros) se le agregan anhídrido succínico (48.2 miligramos, 0.482 milimoles), y trietil-amina (0.112 mililitros, 0.803 milimoles). Después de agitarse

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a temperatura ambiente durante 2 horas, la mezcla de reacción se diluye con EtOAc, y se lava con HCl 1M y salmuera. La capa orgánica se seca sobre Na_2SO_4 y se concentra. El residuo se purifica mediante HPLC en fase inversa (SunFire C18, ácido trifluoro-acético al 0.1 por ciento en H_2O/CH_3CN), para dar el ácido N-[(R)-1-(3'-cloro-bifenil-4-il-metil)-3-metan-sulfonil-amino-3-oxo-propil]-succinámico (63 miligramos). HPLC tiempo de retención = 1.32 minutos (condición A); MS (m+1) = 467; ^{1}H RMN (400 Mz, DMSO-d6) δ ppm 2.22-2.29 (m, 2 H), 2.32-2.54 (m, 4 H), 2.77 (d, 2 H, J = 6.82 Hz), 3.17 (s, 3 H), 4.31 (dt, 1 H, J = 7.33, 13.9 Hz), 7.28 (d, 2 H, J = 8.08 Hz), 7.38-7.43 (m, 1 H), 7.48 (t, 1 H, J = 7.83 Hz), 7.62 (d, 3 H, J = 8.34 Hz), 7.70 (t, 1 H, J = 2.02 Hz), 7.89 (d, 1 H, J = 8.34 Hz), 11.70 (s, 1 H), 12.04 (s, 1 H).

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 16-1:

Ejemplo #	Producto	Material de partida	HPLC-RT (condición)	MS (M+1)
Ejemplo 16-2	 ácido N-[(R)-1-(3'-cloro-bifenil-4-il-		1.26 minutos. (condición A)	495

Ejemplo #	Producto	Material de partida	HPLC-RT (condición)	MS (M+1)
	metil)-3-oxo-3-(propan-1-sulfonil-amino)-propil]-succinámico			
Ejemplo 16-3	 ácido N-[(R)-1-(3'-cloro-bifenil-4-il-metil)-3-oxo-3-fenil-metan-sulfonil-amino-propil]-succinámico		1.34 minutos. (condición A)	543
Ejemplo 16-4			1.33 minutos. (condición A)	389

Ejemplo #	Producto	Material de partida	HPLC-RT (condición)	MS (M+1)
	ácido N-[(R)-2-carbamoil-1-(3'-cloro-bifenil-4-il-metil)-etil]-succinámico			

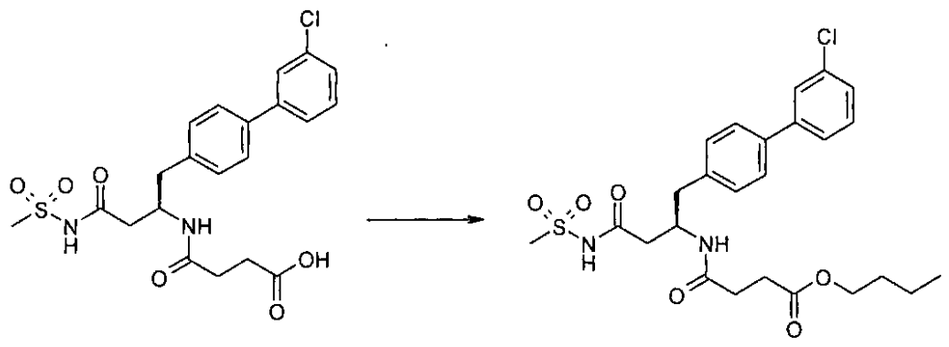
Ejemplo 16-2: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 0.96 (t, 3 H, *J* = 7.33 Hz), 1.66 (dd, 2 H, *J* = 7.33, 15.2 Hz), 2.25 (t, 2 H, *J* = 7.07 Hz), 2.31-2.45 (m, 4 H), 2.76 (d, 2 H, *J* = 6.82 Hz), 3.25-3.32 (m, 2 H), 4.30 (dd, 1 H, *J* = 7.83, 14.7 Hz), 7.28 (d, 2 H, *J* = 8.34 Hz), 7.38-7.43 (m, 1 H), 7.48 (t, 1 H, *J* = 7.83 Hz), 7.63 (d, 3 H, *J* = 8.08 Hz), 7.70 (t, 1 H, *J* = 1.77 Hz), 7.89 (d, 1 H, *J* = 8.34 Hz), 11.61 (s, 1 H), 12.04 (s, 1 H).

Ejemplo 16-3: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.24-2.31 (m, 2 H), 2.34-2.40 (m, 2 H), 2.44 (d, 2 H, *J*= 6.82 Hz), 2.78 (d, 2 H, *J* = 6.82 Hz), 4.26-4.36 (m, 1 H), 4.67 (s, 2 H), 7.25-7.33 (m, 4 H), 7.34-7.43 (m, 4 H), 7.48 (t, 1 H, *J* = 7.58 Hz), 7.63 (d, 3 H, *J* = 8.34 Hz), 7.70 (t, 1 H, *J* = 1.77 Hz), 7.92 (d, 1 H, *J* = 8.34 Hz), 11.60 (s, 1 H), 12.05 (s, 1 H).

Ejemplo 16-4: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.19-2.29 (m, 4H), 2.36 (dd, 2H, *J* = 6.57, 6.57 Hz), 2.72 (dd, 1H, *J*= 7.83, 13.6

Hz), 2.81 (dd, 1H, *J* = 5.31, 13.6 Hz), 4.17-4.27 (m, 1H), 6.83 (s, 1H), 7.28 (d, 3H, *J* = 8.34 Hz), 7.38-7.43 (m, 1H), 7.47 (t, 1H, *J* = 7.83 Hz), 7.58-7.65 (m, 3H), 7.69 (t, 1H, *J* = 1.77 Hz), 7.78 (d, 1H, *J* = 8.34 Hz), 12.05 (s, 1H).

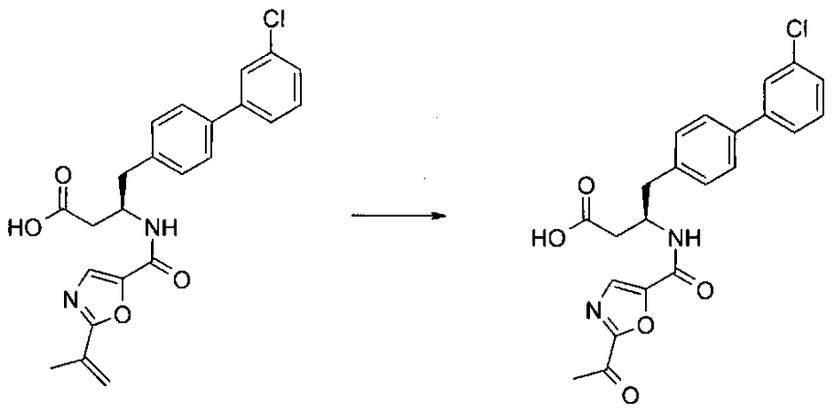
Ejemplo 16-5: Síntesis de butil-éster del ácido N-[(R)-1-(3'-cloro-bifenil-4-il-metil)-3-metan-sulfonil-amino-3-oxo-propil]-succinámico



A una solución de ácido N-[(R)-1-(3'-cloro-bifenil-4-il-metil)-3-metan-sulfonil-amino-3-oxo-propil]-succinámico (50 miligramos, 0.107 milimoles) en butanol normal (2 mililitros), se le agrega cloruro de tionilo (9.38 microlitros, 0.128 milimoles). La mezcla de reacción se calienta a 50°C, y se agita durante 1 hora. Después de enfriar a temperatura ambiente, la mezcla de reacción se concentra y se purifica mediante HPLC en fase inversa (SunFire C18, ácido trifluoro-acético al 0.1 por ciento en H_2O/CH_3CN), para dar el butil-éster del ácido N-[(R)-1-(3'-cloro-bifenil-4-il-metil)-3-metan-sulfonil-amino-3-oxo-propil]-succinámico (32 miligramos). HPLC tiempo de retención = 1.56 minutos (condición A); MS (m+1) = 523; ^{1}H RMN (400 Mz, DMSO-d6) δ ppm 0.86 (t, 3H, *J* = 7.33 Hz), 1.22-1.34 (m, 2H), 1.45-

1.55 (m, 2H), 2.23-2.33 (m, 2H), 2.35-2.44 (m, 3H), 2.45-2.55 (m, 3H), 2.71-2.83 (m, 1H), 3.18 (s, 3H), 3.96 (t, 2H, *J* = 6.57 Hz), 4.27-4.38 (m, 1H), 7.28 (d, 2H, *J* = 8.08 Hz), 7.37-7.43 (m, 1H), 7.48 (t, 1H *J* = 7.83 Hz), 7.62 (d, 3H, *J* = 8.34 Hz), 7.70 (s, 1H), 7.91 (d, 1H, *J* = 8.34 Hz), 11.71 (s, 1H).

Ejemplo 17: Ácido (R)-3-(2-acetil-oxazol-5-carboxamido)-4-(3'-cloro-bifenil-4-il)-butanoico

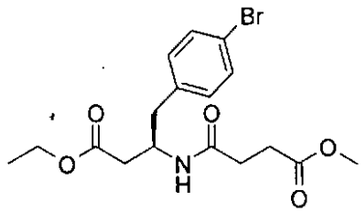


A una solución de ácido (R)-4-(3'-cloro-bifenil-4-il)-3-(2-(prop-1-en-2-il)-oxazol-5-carboxamido)-butanoico (60 miligramos, 0.14 milimoles) en dicloro-metano (2 mililitros) y metanol (2 mililitros) a -78°C, se le burbujea ozono durante 30 segundos. Después de 30 segundos, se remueve el ozono, y se burbujea oxígeno durante 10 minutos. Después de burbujear oxígeno durante 10 minutos se remueve el baño a -78°C, y la reacción se apaga con trifenil-fosfina soportada por polímero, y la reacción se agita a temperatura ambiente durante 2 horas. Después de 2 horas, la reacción se filtra para remover el óxido de trifenil-fosfina sobre el polímero soportado, y el filtrado se recolecta y se concentra bajo presión reducida. El

residuo obtenido se purifica mediante HPLC de fase inversa (SunFire C18, H_2O (ácido trifluoro-acético al 0.1 por ciento)/CH_3CN), y se liofiliza, para dar el ácido (R)-3-(2-acetil-oxazol-5-carboxamido)-4-(3'-cloro-bifenil-4-il)-butanoico (13 miligramos). HPLC - tiempo de retención = 1.67 minutos (condición D); MS (m+1) = 427.0; ^{1}H RMN (400 MHz, DMSO-d_6) δppm 2.53 - 2.59 (m, 2 H) 2.60 (s, 3 H) 2.87 (dd, *J*=10.9, 3.3 Hz, 1 H) 2.94 (dd, *J*=10.9, 5.1 Hz, 1 H) 4.46 - 4.60 (m, 1 H) 7.31 (d, *J*=8.1 Hz, 2 H) 7.36 - 7.43 (m, 1 H) 7.47 (t, *J*=7.8 Hz, 1 H) 7.62 (d, *J*=8.3 Hz, 3 H) 7.69 (t, *J*=1.9 Hz, 1 H) 7.94 (s, 1 H) 8.86 (d, *J*=8.6 Hz, 1 H) 12.31 (br. s., 1 H).

Los materiales de partida o intermediarios se preparan de la siguiente manera:

Intermediario 1: 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo

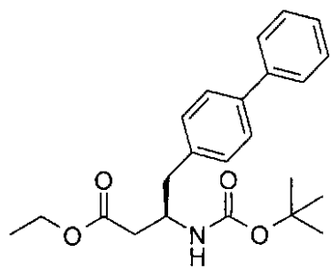


Al 4-(4-bromo-fenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-etilo (2.02 gramos, 5.23 milimoles), se le agrega una solución de HCl 4M en 1,4-dioxano (13.1 mililitros, 52.3 milimoles) a temperatura ambiente. Después de agitar durante 1 hora, la mezcla de reacción se concentra bajo presión reducida, para dar el clorhidrato de etil-éster del ácido (R)-3-amino-4-bromo-fenil-4-il-butírico. A una solución del clorhidrato de etil-éster del ácido (R)-3-

amino-4-bromo-fenil-4-il-butírico, se le agregan anhídrido succínico (0.707 gramos, 7.06 milimoles), y di-isopropil-etil-amina (2.06 mililitros, 11.8 milimoles) en dicloro-metano (20 mililitros), y se deja agitándose durante 4 horas. La reacción se apaga con HCl acuoso 0.1 M. Los productos se extraen con acetato de etilo, y se lavan con salmuera. La capa orgánica se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida, para dar el ácido (R)-4-(1-(4-bromo-fenil)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico (2.26 gramos). A una solución del residuo obtenido (2.26 gramos) en tolueno (25 mililitros) y metanol (25 mililitros), se le agrega en porciones $TMSCHN_2$ en hexanos (5.85 mililitros, 11.70 milimoles), a temperatura ambiente bajo nitrógeno. La mezcla de reacción se deja agitándose durante 1.5 horas, entonces se apaga con AcOH (0.5 mililitros; 8.78 milimoles), y la solución se agita durante 10 minutos. La solución se concentra, y el residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea sobre 40 gramos de gel de sílice (eluyente: heptano/EtOAc = 100:0 a 0:100), para dar el 4-(4-bromo-fenil)-3-(4-metoxi-4-oxo-butanamido)-butanoato de (R)-etilo (1.92 gramos). HPLC - tiempo de retención = 1.04 minutos (condición B); MS (ES+) = 400 (m+1), 402.0 (m+3; 100 por ciento); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, *J*=7.2 Hz, 3 H) 2.40 - 2.53 (m, 4 H) 2.60 - 2.64 (m, 2 H) 2.79 (A de ABX, Jab = 13.7 Hz, Jax = 7.85 Hz, 1 H) 2.90 (B de ABX, Jab = 13.7 Hz, Jbx = 6.65 Hz, 1 H) 3.68 (s, 3 H) 4.10 – 4.22 (m, 2 H) 4.39 – 4.47 (m, 1 H) 6.29 (br d, J = 8.6 Hz, 1 H) 7.06 (d, J = 8.4 Hz, 2 H) 7.40 –

7.42 (m, 2 H).

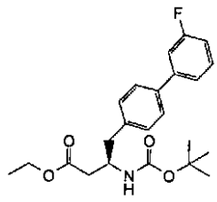
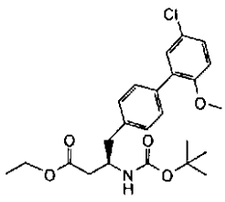
Intermediario 2: 4-(bifenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-etilo

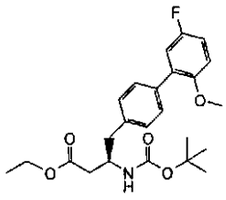
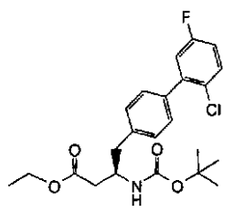


Una mezcla de 4-(4-bromo-fenil)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-etilo (1.5 gramos, 3.88 milimoles), ácido fenil-borónico (0.710 gramos, 5.82 milimoles), $Pd(Ph_3P)_4$ (0.449 gramos, 0.388 milimoles), y Na_2CO_3 acuoso (3.88 mililitros, 7.77 milimoles) en tolueno (25 mililitros), se deja agitándose a 95°C bajo nitrógeno durante 14 horas. La mezcla de reacción se enfría a temperatura ambiente, y se apaga con salmuera. La mezcla se extrae dos veces con acetato de etilo, y la capa orgánica combinada se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea en gel de sílice (heptano/EtOAc = 100:0 a 50:50), para dar el 4-(bifenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-etilo (1.30 gramos); HPLC - tiempo de retención = 1.61 minutos (condición B); MS (ES+) = 328.0 (m-tBu+2); 284.1 (m-Boc+2; 100 por ciento); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, J = 7.1 Hz, 3 H) 2.48 (A de ABX, Jab = 16.1 Hz, Jax = 5.9 Hz, 1 H) 2.53 (B de ABX, Jab = 16.0

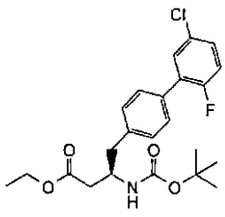
Hz, Jbx = 5.3 Hz, 1 H) 2.83 – 3.00 (m, 2 H) 4.14 – 4.19 (m, 3 H) 5.06 (br s) 7.26 – 7.27 (m, 2 H) 7.31-7.35 (m, 2 H) 7.43 (t, J = 7.6 Hz, 2H) 7.52 -7.58 (m, 4 H).

Los siguientes intermediarios se preparan empleando un procedimiento similar al que se describe para el intermediario 2:

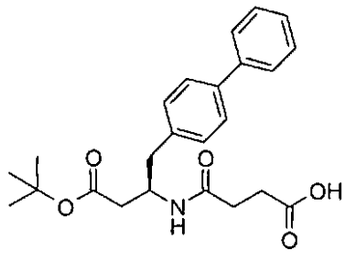
Intermediario #	Producto	Condición	HPLC-RT (condición)	MS (ES+; 100%)
Intermediario 2-2	 3-(terbutoxicarbonil-amino)-4-(3'-fluoro-bifenil-4-il)-butanoato de (R)-etilo	$Pd(PPh_3)_4$, ácido 3-fluoro-bencen-borónico, Na_2CO_3 acuoso 2M, tolueno, 95°C	1.61 minutos. (B)	302.1 (m-BOC+2)
Intermediario 2-3	 3-(terbutoxicarbonil-amino)-4-(5'-cloro-2'-metoxi-bifenil-4-	$PdCl_2(dppf)$. Complejo de CH_2Cl_2, ácido 5-cloro-2-metoxi-fenil-borónico, Na_2CO_3 acuoso 2M, tolueno,	1.58 minutos. (B)	348.1 (m-BOC+2)

Interme-diario #	Producto	Condición	HPLC-RT (condición)	MS (ES+; 100%)
	il)-butanoato de (R)-etilo	95°C		
Interme-diario 2-4	 3-(terbutoxi-carbonil-amino)-4-(5'-fluoro-2'-metoxi-bifenil-4-il)-butanoato de (R)-etilo	$PdCl_2(dppf)$. Complejo de CH_2Cl_2, ácido 5-fluoro-2-metoxi-fenil-borónico, Na_2CO_3 acuoso 2M, tolueno, 95°C	1.42 minutos. (B)	332.2 (m-BOC+2)
Interme-diario 2-5	 3-(terbutoxi-carbonil-amino)-4-(2'-cloro-5'-fluoro-bifenil-4-il)-butanoato de (R)-	$Pd(PPh_3)_4$, ácido 2-cloro-5-fluoro-fenil-borónico, Na_2CO_3 acuoso 2M, tolueno, 95°C	1.49 minutos. (B)	336.1 (m-BOC+2)

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Interme-diario #	Producto	Condición	HPLC-RT (condición)	MS (ES+; 100%)
	etilo			
Interme-diario 2-6	 3-(terbutoxi-carbonil-amino)-4-(5'-cloro-2'-fluoro-bifenil-4-il)-butanoato de (R)-etilo	$Pd(PPh_3)_4$, ácido 5-cloro-2-fluoro-fenil-borónico, Na_2CO_3 acuoso 2M, DME, 95°C	1.47 minutos. (B)	336.1 (m-BOC+2)

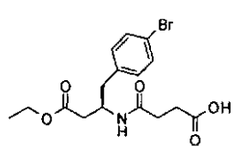
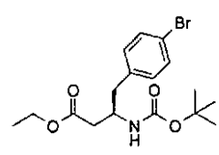
Intermediario 3: Ácido (R)-4-(1-(bifenil-4-il)-4-terbutoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico



Al 4-(bifenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-terbutilo (26.4 miligramos, 0.064 milimoles), se le agrega HCl 4M en 1,4-dioxano (0.321 mililitros, 1.283 milimoles) a temperatura

ambiente. La mezcla de reacción se agita durante 45 minutos, y se concentra bajo presión reducida. A una solución del residuo obtenido en dicloro-metano (0.4 mililitros), se le agrega anhídrido succínico (7.70 miligramos, 0.077 milimoles), y di-isopropil-etil-amina (0.013 mililitros, 0.077 milimoles). La mezcla de reacción se deja agitándose a temperatura ambiente durante 14 horas, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante HPLC de fase inversa (SunFire C-18, H_2O (ácido trifluoro-acético al 0.1 por ciento)/CH_3CN), para dar el ácido (R)-4-(1-(bifenil-4-il)-4-terbutoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoico (9.5 miligramos). HPLC - tiempo de retención = 1.70 minutos (condición A); MS (ES+) = 412.1 (m+1); 356.0 (m-tBu+2; 100 por ciento); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.48 (s, 9 H) 2.36 -2.51 (m, 4 H) 2.64 – 2.67 (m, 2 H) 2.87 (A de ABX, Jab = 13.5 Hz, Jax = 5.7 Hz, 1 H), 2.97 (Jab = 13.5 Hz, Jbx = 6.2 Hz, 1 H) 7.24-7.26 (m, 2 H) 7.31-7.35 (m, 1 H) 7.43 (t, J = 7.75 Hz, 2 H) 7.53(d, J = 8.0 Hz, 2 H) 7.57 (d, J = 7.6 HZ, 2 H).

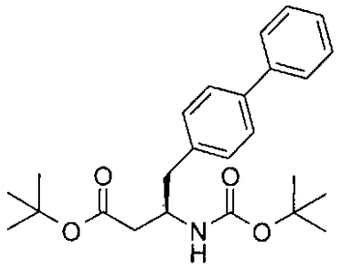
Los siguientes intermediarios se preparan empleando un procedimiento similar al que se describe para el intermediario 3:

Interme-diario #	**Producto**	**Material de partida**	**HPLC-RT (condición)**	**MS (M+1)**
Intermediario 3-2			0.90 minutos. (B)	385.9

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Interme-diario #	Producto	Material de partida	HPLC-RT (condición)	MS (M+1)
	etil-éster del ácido (R)-4-(4-bromo-fenil)-3-(3-carboxi -propionil-amino)-butírico			

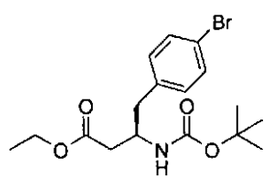
Intermediario 4: 4-(bifenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-terbutilo



Una solución del ácido (R)-2-(bifenil-4-il-metil)-4-terbutoxi-4-oxo-butanoico (100 miligramos, 0.294 milimoles), DPPA (0.076 mililitros, 0.353 milimoles), y Et_3N (0.049 mililitros, 0.353 milimoles) en tolueno (1.5 mililitros), se deja agitándose a 100°C bajo nitrógeno durante 2 horas. Se agrega tBuOH (0.281 mililitros, 2.94 milimoles), y la mezcla se pone a reflujo durante 5 horas a la misma temperatura. La reacción se enfría a temperatura ambiente, y el solvente se remueve. Se agrega acetato de etilo al residuo obtenido,

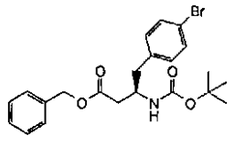
y la capa orgánica se lava con ácido cítrico acuoso al 5 por ciento, H_2O, $NaHCO_3$ acuoso saturado, y salmuera. La capa orgánica se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea sobre 40 gramos de gel de sílice (heptano/EtOAc = 100:0 a 50:50), para dar el isocianato correspondiente (35.7 miligramos). El isocianato obtenido se disuelve en tBuOH (0.3 mililitros), y la solución se deja agitándose a 80°C durante 20 horas. La mezcla de reacción se concentra, y el residuo se purifica mediante cromatografía en columna por evaporación instantánea sobre 12 gramos de gel de sílice (heptano/EtOAc = 100:0 a 70:30), para dar el 4-(bifenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-terbutilo (26.4 miligramos, 22 por ciento). HPLC - tiempo de retención = 1.74 minutos (condición B); MS (ES+) = 356.0 (m-tBu+2) 300.0 (m-tBux2+3; 100 por ciento); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.41 (s, 9 H) 1.47 (s, 9 H) 2.36 (A de ABX, Jab = 15.6 Hz, Jax = 6.2 Hz, 1 H) 2.44 (B de ABX, Jab = 15.5 Hz, Jbx = 5.45 Hz) 2.82 – 2.97 (m, 2 H) 4.15 (br s) 5.09 (br d) 7.6-7.35 (m, 3H) 7.41 – 7.45 (m, 2 H) 7.51-7.56 (m, 4 H).

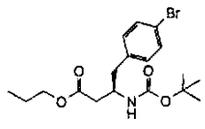
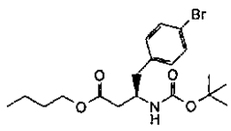
Intermediario 5: 4-(4-bromo-fenil)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-etilo



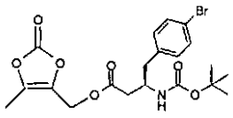
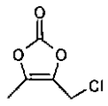
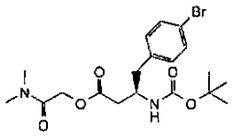
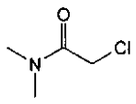
A una suspensión del ácido (R)-4-(4-bromo-fenil)-3-(terbutoxi-carbonil-amino)-butanoico (9.98 gramos, 27.9 milimoles), y $NaHCO_3$ (4.68 gramos, 55.7 milimoles) en N,N-dimetil-formamida (45 mililitros), se le agrega yoduro de etilo (6.75 mililitros, 84 milimoles) a temperatura ambiente bajo nitrógeno. Después de agitar durante 71 horas, la reacción se apaga con H_2O (300 mililitros), y entonces el sólido precipitado se recolecta y se lava con H_2O (500 mililitros), para dar el 4-(4-bromo-fenil)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-etilo (10.25 gramos, 94 por ciento). HPLC - tiempo de retención = 1.48 minutos (condición B); MS (ES+) = 329.9 (m-tBu+2); 286.0 (m-Boc+2; 100 por ciento); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.27 (t, J = 7.2 Hz, 3 H) 1.40 (s, 9 H), 2.43 (A de ABX, Jab = 15.8 Hz, Jax = 5.7 Hz, 1 H) 2.50 (B de ABX, Jab = 15.8 Hz, Jbx = 5.4 Hz, 1 H) 2.74 – 2.90 (m, 2 H) 4.11 (br s) 4.15 (q, J = 7.1 Hz, 2 H) 5.04 (br d) 7.07 (d, J = 8.3 Hz, 2 H) 7.40-7.43 (m, 2 H).

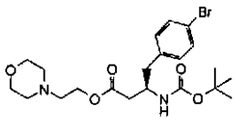
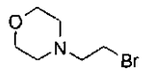
Los siguientes intermediarios se preparan empleando un procedimiento similar al que se describe para el intermediario 5:

Interme-diario #	**Producto**	**Condición**	**HPLC-RT (condición)**	**MS (ES+; 100%)**
Interme-diario 5-2	 4-(4-bromo-fenil)-3-	BnBr, $NaHCO_3$, N,N-dimetil-formamida, RT	1.56 minutos. (B)	348 (m-BOC+2)

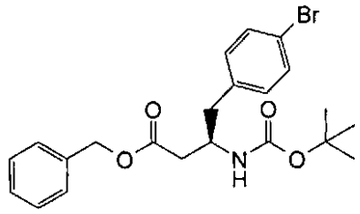
Interme-diario #	Producto	Condición	HPLC-RT (condición)	MS (ES+; 100%)
	(terbutoxi-carbonil-amino)-butanoato de (R)-bencilo			
Interme-diario 5-3	 propil-éster del ácido (R)-4-(4-bromo-fenil)-3-terbutoxi-carbonil-amino-butírico	yoduro de n-propilo, $NaHCO_3$, N,N-dimetil-formamida, RT	1.47 minutos. (B)	400 (m+1)
Interme-diario 5-4	 butil-éster del ácido (R)-4-(4-bromo-fenil)-3-terbutoxi-carbonil-amino-butírico	yoduro de n-butilo, $NaHCO_3$, N,N-dimetil-formamida, RT	1.55 minutos. (B)	414 (m+1)

315

Intermediario #	Producto	Condición	HPLC-RT (condición)	MS (ES+; 100%)
Intermediario 5-5	 5-metil-2-oxo-[1,3]-dioxol-4-il-metil-éster del ácido (R)-4-(4-bromo-fenil)-3-terbutoxi-carbonil-amino-butírico	 K_2CO_3, N,N-dimetil-formamida, RT	1.28 minutos. (B)	470 (m+1)
Intermediario 5-6	 dimetil-carbamoil-metil-éster del ácido (R)-4-(4-bromo-fenil)-3-terbutoxi-carbonil-amino-butírico	 K_2CO_3, N,N-dimetil-formamida, RT	1.65 minutos. (B)	444 (m+1)

Interme-diario #	Producto	Condición	HPLC-RT (condición)	MS (ES+; 100%)
Interme-diario 5-7	 2-morfolin-4-il-etil-éster del ácido (R)-4-(4-bromo-fenil)-3-terbutoxi-carbonil-amino-butírico	 K_2CO_3, N,N-dimetil-formamida, RT	1.19 minutos. (B)	471 (m+1)

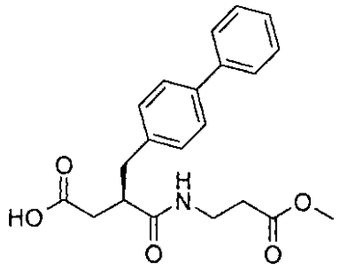
Intermediario 5-2: 4-(4-bromo-fenil)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-bencilo



A una suspensión del ácido (R)-4-(4-bromo-fenil)-3-(terbutoxi-carbonil-amino)-butanoico (5.02 gramos, 14.01 milimoles), y $NaHCO_3$ (3.53 gramos, 42.0 milimoles) en N,N-dimetil-formamida (20 mililitros), se le agrega bromuro de bencilo (5.10 mililitros, 42 milimoles) a temperatura ambiente bajo nitrógeno. Después de agitar

durante 46 horas, la reacción se diluye con H_2O (200 mililitros), y entonces el sólido precipitado se recolecta y se lava con H_2O (500 mililitros), y entonces con heptano (200 mililitros), para dar el 4-(4-bromo-fenil)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-bencilo (5.61 gramos, 89 por ciento). HPLC - tiempo de retención = 1.56 minutos (condición B); MS (ES+) = 392.1 (m-tBu+2); 348.1 (m-Boc+2; 100 por ciento); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.39 (s, 9 H) 2.48 (A de ABX, Jab = 15.9 Hz, Jax = 5.6 Hz, 1 H) 2.54 (B de ABX, Jab = 15.9 Hz, Jbx = 5.3 Hz, 1 H) 2.72 – 2.88 (m, 2 H) 4.11 (br s, 1 H) 5.02 (br s, 1 H) 5.10 (A de AB, J = 12.1 Hz, 1 H) 5.16 (A de AB, J = 12.1 Hz, 1 H) 7.00 (d, J = 8.1 Hz, 2 H) 7.34-7.39 (m, 7 H).

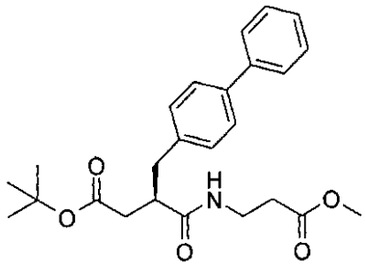
Intermediario 6: Ácido (R)-3-(bifenil-4-il-metil)-4-(3-metoxi-3-oxopropil-amino)-4-oxo-butanoico



A una solución del 3-(bifenil-4-il-metil)-4-(3-metoxi-3-oxopropil-amino)-4-oxo-butanoato de (R)-terbutilo (40 miligramos, 0.094 milimoles) en dicloro-metano (0.5 mililitros), se le agrega ácido trifluoro-acético (0.15 mililitros) a temperatura ambiente. La mezcla se deja agitándose durante 2 horas, y entonces se concentra bajo presión reducida, para dar el ácido (R)-3-(bifenil-4-il-metil)-4-(3-metoxi-3-oxopropil-amino)-4-oxo-butanoico (33.5 miligramos, 96 por ciento).

HPLC - tiempo de retención = 1.20 minutos (condición A); MS (m+1) = 370.1; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 2.21 – 2.29 (m, 1 H) 2.38 – 2.45 (m, 1 H) 2.62 – 2.66 (m, 1 H) 2.75 – 3.00 (m,4 H) 3.29 – 3.37 (m, 1 H) 3.45 – 3.53 (m, 4 H) 6.12 (br s, 1 H) 7.23 (d, J = 8 Hz, 2 H) 7.32 – 7.35 (m, 1 H) 7.41 -7.45 (m, 2 H) 7.53 (d, J = 8.1 Hz, 2 H) 7.56 – 7.59 (m, 2 H).

Intermediario 7: 3-(bifenil-4-il-metil)-4-(3-metoxi-3-oxopropil-amino)-4-oxo-butanoato de (R)-terbutilo

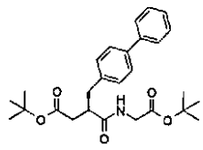
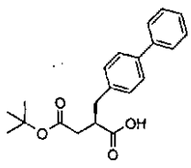
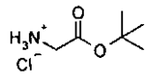


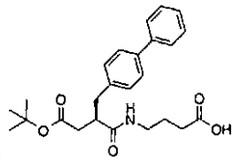
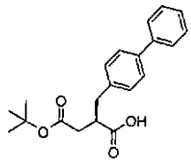
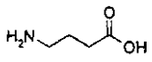
Una solución del ácido (R)-2-(bifenil-4-il-metil)-4-terbutoxi-4-oxo-butanoico (142 miligramos, 0.417 milimoles), clorhidrato de metil-éster del ácido 3-amino-propiónico (76 miligramos, 0.542 milimoles), clorhidrato de WSC (120 miligramos, 0.626 milimoles), 1-hidroxi-7-azabenzotriazol (85 miligramos, 0.626 milimoles), y di-isopropil-etil-amina (0.219 mililitros, 1.251 milimoles) en N,N-dimetil-formamida (4 mililitros), se deja agitándose a temperatura ambiente bajo nitrógeno durante 13 horas. La reacción se apaga con H_2O. Los productos se extraen con acetato de etilo, se lavan con HCl acuoso 1M, y entonces con salmuera, se secan sobre Na_2SO_4, se filtran, y se concentran bajo presión reducida. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea

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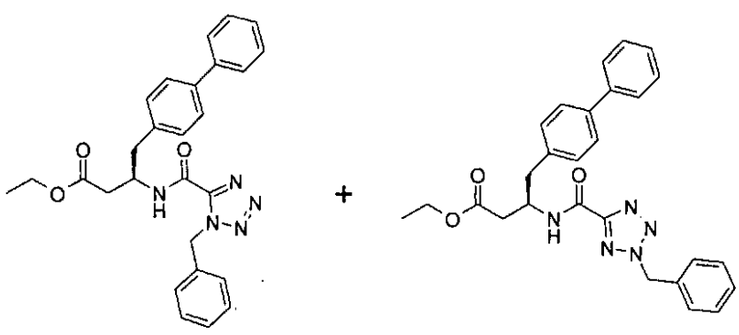
sobre 12 gramos de gel de sílice (heptano/EtOAc = 70:30 a 0:100), para dar el 3-(bifenil-4-il-metil)-4-(3-metoxi-3-oxopropil-amino)-4-oxo-butanoato de (R)-terbutilo (164 miligramos, 91 por ciento). HPLC - tiempo de retención = 1.59 minutos (condición A); MS (ES+) = 425.4 (m); 369.4 (m-tBu+1; 100 por ciento); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 2.24 – 2.44 (m, 2 H) 2.67 -2.79 (m, 3 H) 2.89 -2.96 (m, 1 H) 3.28 – 3.36 (m, 1 H) 3.45 – 3.53 (m, 1 H) 7.23 (d, J = 5.8 Hz, 2 H) 7.33 (t, J = 7.35 Hz, 1 H) 7.41 – 7.44 (m, 2 H) 7.51 (d, J = 8.1 Hz, 2 H) 7.58 (d, J = 7.4 Hz, 2 H).

Los siguientes intermediarios se preparan empleando un procedimiento similar al que se describe para el intermediario 7:

Interme-diario #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
Interme-diario 7-2	 terbutil-éster del ácido (R)-3-bifenil-4-il-metil-N-terbutoxi-carbonil-metil-succinámico		 WSC.HCl, HOAt, DIPEA, N,N-dimetil-formamida, rt	1.64 minutos. (B)	454.1

Interme-diario #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
Interme-diario 7-3	 terbutil-éster del ácido (R)-3-bifenil-4-il-metil-N-(3-carboxi-propil)-succinámico		 WSC.HCl, HOAt, DIPEA, N,N-dimetil-formamida, rt	1.71 minutos. (A)	426.1

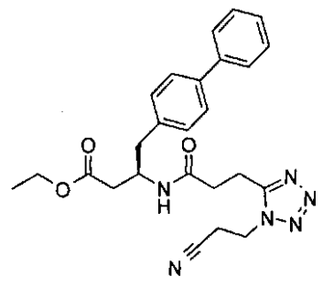
Intermediario 8: Etil-éster del ácido (R)-3-[(1-bencil-1H-tetrazol-5-carbonil)-amino]-4-bifenil-4-il-butírico y etil-éster del ácido (R)-3-[(2-bencil-2H-tetrazol-5-carbonil)-amino]-4-bifenil-4-il-butírico



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El 4-(bifenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-etilo (117 miligramos, 0.305 milimoles), se trata con una solución de HCl 4M en dioxano (2 mililitros). Después de agitar durante 0.5 horas, la mezcla de reacción se concentra bajo presión reducida. A una solución del residuo obtenido y Et_3N (0.106 mililitros, 0.763 milimoles) en dicloro-metano (3 mililitros), se le agrega cloruro de bencil-*H*-tetrazol-5-carbonilo (mezcla de isómeros de 1- y 2-bencilo, 82 miligramos, 0.366 milimoles, preparada de acuerdo con *J.Med.Chem.* **1986**, *29*, 538-549). Después de agitar durante 10 minutos, se agregan Et_3N (0.106 mililitros, 0.763 milimoles), y el cloruro de ácido (82 miligramos, 0.366 milimoles). Después de agitar durante 0.5 horas, la mezcla de reacción se diluye con acetato de etilo, se lava con H_2O y salmuera, se seca sobre Na_2SO_4, y se concentra bajo presión reducida. El residuo se purifica mediante cromatografía en columna de gel de sílice, para dar el etil-éster del ácido (R)-3-[(1-bencil-1H-tetrazol-5-carbonil)-amino]-4-bifenil-4-il-butírico y el etil-éster del ácido (R)-3-[(2-bencil-2H-tetrazol-5-carbonil)-amino]-4-bifenil-4-il-butírico. HPLC - tiempo de retención = 1.51 minutos (condición D); MS = 470.0 (m+1); ^{1}H RMN (400 MHz, CDCl3) δ ppm 1.27 (t, J=7.07, 7.07Hz, 3H), 2.57-2.70 (m, 2H), 3.00 (dd, J=7.58, 13.77Hz, 1H), 3.12 (dd, J=6.57, 13.77Hz, 1H), 4.12-4.23 (m, 2H), 4.71-4.80 (m, 1H), 5.80 (s, 2H), 7.27-7.45 (m, 9H), 7.52 (d, J=8.34Hz, 2H), 7.56 (d, J=8.46Hz, 2H), 7.75 (d, J=7.33Hz, 1H).

Intermediario 9: Etil-éster del ácido (R)-4-bifenil-4-il-3-{3-[1-(2-ciano-etil)-1H-tetrazol-5-il]-propionil-amino}-butírico



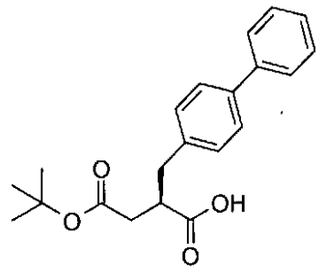
A una solución del etil-éster del ácido (R)-4-bifenil-4-il-3-terbutoxi-carbonil-amino-butírico (400 miligramos, 1.04 milimoles) en dicloro-metano (10 mililitros) a temperatura ambiente, se le agrega ácido trifluoro-acético (2.009 mililitros, 26.1 milimoles), y la mezcla se agita a temperatura ambiente durante 1 hora. La mezcla se concentra bajo presión reducida. A la sal de ácido trifluoro-acético obtenida en dicloro-metano (10 mililitros) a la temperatura del baño de hielo, se le agrega anhídrido succínico (125 miligramos, 1.25 milimoles), seguido por trietil-amina (0.363 mililitros, 2.61 milimoles). La reacción se agita a temperatura ambiente durante 16 horas. La mezcla se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía por evaporación instantánea (gel de sílice, del 2 por ciento al 5 por ciento de EtOH/DCM), para dar el etil-éster del ácido (R)-4-bifenil-4-il-3-(3-carboxi-propionil-amino)-butírico (200 miligramos). HPLC - tiempo de retención = 1.53 minutos (condición C); MS = 384 (m+1).

En seguida, a una solución del etil-éster del ácido (R)-4-bifenil-4-il-3-(3-carboxi-propionil-amino)-butírico (200 miligramos, 0.522 milimoles) en tetrahidrofurano (10 mililitros) a temperatura ambiente, se le agregan EDC HCl (120 miligramos, 0.626 milimoles) y HOBT

(96 miligramos, 0.626 milimoles). La reacción se agita a temperatura ambiente durante 10 minutos, y entonces se agregan 3-amino-propionitrilo (0.046 mililitros, 0.626 milimoles), y trietil-amina (0.087 mililitros, 0.626 milimoles). Después de 1 hora, se agregan 0.5 equivalentes de EDC HCl, HOBT, y 3-amino-propionitrilo, y se agitan durante 16 horas. La mezcla de reacción se apaga con salmuera, y se extrae con acetato de etilo. La capa orgánica combinada se lava con salmuera, y se seca sobre sulfato de sodio anhidro, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía por evaporación instantánea (gel de sílice, del 2 por ciento al 5 por ciento de EtOH/DCM), para dar el etil-éster del ácido (R)-4-bifenil-4-il-3-[3-(2-ciano-etil-carbamoil)-propionil-amino]-butírico (218 miligramos, 96 por ciento de rendimiento). HPLC - tiempo de retención = 0.77 minutos (condición E); MS = 436 (m+1). En seguida, a una solución del etil-éster del ácido (R)-4-bifenil-4-il-3-[3-(2-ciano-etil-carbamoil)-propionil-amino]-butírico (204 miligramos, 0.468 milimoles) en tetrahidrofurano (10 mililitros) a temperatura ambiente, se le agrega Ph_3P (307 miligramos, 1.17 milimoles), y la mezcla se agita a temperatura ambiente durante 10 minutos. Entonces a la mezcla, a una temperatura del baño helada, se le agregan DIAD (0.228 mililitros, 1.171 milimoles), y trimetil-silil-azida (0.155 mililitros, 1.171 milimoles). La mezcla resultante se calienta lentamente hasta la temperatura ambiente, y se agita durante 16 horas. La mezcla de reacción se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía por evaporación

instantánea (gel de sílice, del 1 por ciento al 3 por ciento de EtOH/DCM), para dar el etil-éster del ácido (R)-4-bifenil-4-il-3-{3-[1-(2-ciano-etil)-1H-tetrazol-5-il]-propionil-amino}-butírico (137 miligramos, 64 por ciento de rendimiento). HPLC - tiempo de retención = 1.61 minutos (condición C); MS = 461 (m+1).

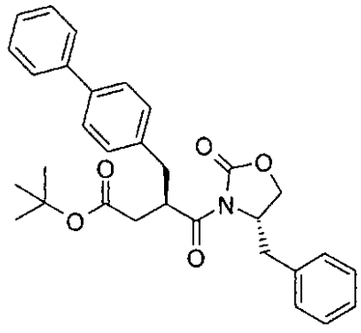
Intermediario 10: Ácido (R)-2-(bifenil-4-il-metil)-4-terbutoxi-4-oxo-butanoico



A una solución agitada del 4-((S)-4-bencil-2-oxo-oxazolidin-3-il)-3-(bifenil-4-il-metil)-4-oxo-butanoato de (R)-terbutilo (1.20 gramos, 2.402 milimoles) en un solvente mixto de tetrahidrofurano (20 mililitros), y agua (5 mililitros), se le agrega una solución de H_2O_2 acuoso (0.960 mililitros, 9.61 milimoles), y LiOH acuoso (4.80 mililitros, 4.80 milimoles) a 0°C durante 5 minutos. Después de agitar durante 1.5 horas, la reacción se apaga con Na_2SO_3 acuoso saturado (10 mililitros) a 0°C, y se deja agitándose durante 10 minutos a la misma temperatura. La mezcla de reacción se calienta hasta la temperatura ambiente con agitación durante 0.5 horas. Entonces, se agregan $NaHCO_3$ acuoso saturado y salmuera a la mezcla. El producto se extrae con acetato de etilo, se lava con HCl 1M acuoso,

se seca sobre $MgSO_4$, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea sobre 120 gramos de gel de sílice (heptano/EtOAc = 75:25 a 0:100), para dar el ácido (R)-2-(bifenil-4-il-metil)-4-terbutoxi-4-oxo-butanoico (765 miligramos, 93 por ciento). HPLC - tiempo de retención = 1.63 minutos (condición D); MS = 338.6 (m-1); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.43 (s, 9 H) 2.41 (A de ABX, J_{ab}=16.67 Hz, J_{ax} = 4.55 Hz, 1 H) 2.52 - 2.67 (B de ABX, Jab = 16.75 Hz, Jbx = 8.45 Hz, 1 H) 2.74 - 2.89 (m, 1 H) 3.06 - 3.22 (m, 2 H) 7.22 - 7.29 (m, 2 H) 7.30 - 7.37 (m, 1 H) 7.43 (t, *J*=7.58 Hz, 2 H) 7.53 (d, *J*= 8.1 Hz, 2 H) 7.57 (d, J = 7.8 Hz, 2 H).

Intermediario 11: Síntesis de 4-((S)-4-bencil-2-oxo-oxazolidin-3-il)-3-(bifenil-4-il-metil)-4-oxo-butanoato de (R)-terbutilo

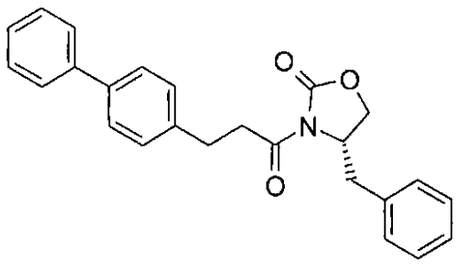


Una solución agitada de la (S)-4-bencil-3-(3-(bifenil-4-il)-propanoil)-oxazolidin-2-ona (intermediario 12: 5.01 gramos, 13.00 milimoles) en tetrahidrofurano (180 mililitros), se enfría a -73.8°C, y se agrega una solución 1M en tetrahidrofurano de hexametil-disilil-amida de sodio (14.30 mililitros, 14.30 milimoles), durante 5 minutos.

Después de 30 minutos, se agrega por goteo una solución de bromo-acetato de terbutilo (2.495 mililitros, 16.90 milimoles) en tetrahidrofurano (20 mililitros), durante 5 minutos. La solución se agita a -74°C durante 1 hora, y la reacción se apaga con NH_4Cl acuoso saturado (100 mililitros), y se calienta hasta la temperatura ambiente. El sólido precipitado se filtra y se lava con acetato de etilo (50 mililitros). La fase orgánica se separa, se lava con salmuera, se seca sobre $MgSO_4$, y se concentra bajo presión reducida. El residuo obtenido se suspende en metanol (70 mililitros), y entonces se filtra para recolectar el sólido (5.9 gramos) como una mezcla del producto deseado y el material de partida. La mezcla se purifica mediante cromatografía en columna por evaporación instantánea sobre 120 gramos de gel de sílice (heptano/EtOAc = 90:10 a 50:50), para dar el 4-((S)-4-bencil-2-oxo-oxazolidin-3-il)-3-(bifenil-4-il-metil)-4-oxo-butanoato de (R)-terbutilo (2.40 gramos, 37 por ciento). HPLC - tiempo de retención = 1.74 minutos (condición B); MS = 499.4 (m+); 443.4 (m-tBu+1; 100 por ciento); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.41 (s, 9 H) 2.42 (dd, *J*=16.67, 4.04 Hz, 1 H) 2.71 (ddd, *J*=16.55, 13.26, 9.60 Hz, 2 H) 2.87 (dd, *J*=16.93, 10.86 Hz, 1 H) 3.04 (dd, *J*=13.14, 6.32 Hz, 1 H) 3.32 (dd, *J*=13.39, 3.03 Hz, 1 H) 3.92 (t, *J*=8.34 Hz, 1 H) 4.07 (dd, *J*=8.97, 2.15 Hz, 1 H) 4.48 - 4.58 (m, 2 H) 7.20 - 7.30 (m, 3 H) 7.30 - 7.36 (m, 5 H) 7.42 (t, *J*=7.58 Hz, 2 H) 7.52 (d, J = 8.1 Hz, 2 H) 7.56 (d, J = 7.8 Hz, 2 H).

Intermediario 12: (S)-4-bencil-3-(3-(bifenil-4-il)-propanoil)-oxazolidin-2-ona

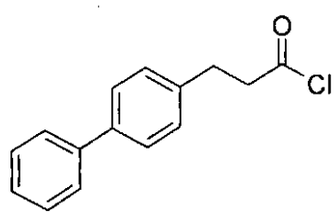
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A una solución 1.6 M de n-BuLi en hexano (12.1 mililitros, 19.3 milimoles), se le agrega por goteo una solución de (*S*)-(-)-4-bencil-2-oxazolidinona (3.26 gramos, 18.4 milimoles) en tetrahidrofurano seco (80 mililitros) a -71.6°C bajo nitrógeno durante 10 minutos. La solución se calienta hasta -60.5°C durante la adición, y se deja agitándose durante 1 hora en un baño de hielo seco/MeOH. Se agrega por goteo cloruro de 3-(bifenil-4-il)-propanoílo (intermediario 13: 5.46 gramos, 22.31 milimoles) en tetrahidrofurano seco (20 mililitros), a -72°C durante 5 minutos. La solución se calienta hasta -56.5°C durante la adición. Después de agitar durante 10 minutos a la misma temperatura, la mezcla de reacción se deja calentar a temperatura ambiente, y la agitación se continúa durante 3 horas. La mezcla de reacción se filtra, y el precipitado recolectado se lava con 20 mililitros (10 mililitros, 2 veces) de metanol, y entonces con 150 mililitros de H_2O, para dar el producto deseado (4.26 gramos). Los productos del licor madre se extraen con acetato de etilo, se lavan con salmuera, se secan sobre $MgSO_4$, se filtran, y se concentran bajo presión reducida. El residuo obtenido se suspende en 80 mililitros de MeOH, y la suspensión se filtra y se lava con 20 mililitros de metanol (1.79 gramos). Las dos fracciones se mezclan

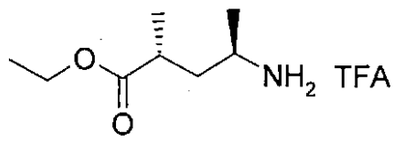
para dar la (S)-4-bencil-3-(3-(bifenil-4-il)-propanoil)-oxazolidin-2-ona (6.05 gramos, 85 por ciento en 2 pasos). Tiempo de retención = 1.77 minutos (condición A); MS (m+1) = 387.3; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 2.77 (dd, *J*=13.39, 9.35 Hz, 1 H) 2.99 - 3.15 (m, 2 H) 3.20 - 3.43 (m, 3 H) 4.09 - 4.24 (m, 2 H), 4.68 (dddd, *J*=9.76, 6.73, 3.47, 3.28 Hz, 1 H) 7.18 (d, *J*=7.07 Hz, 2 H) 7.23 - 7.37 (m, 6 H) 7.42 (t, *J*=7.58 Hz, 2 H) 7.53 (d, J = 8.1 Hz, 2 H), 7.57 (d, J = 7.8 Hz, 2 H).

Intermediario 13: Cloruro de 3-(bifenil-4-il)-propanoílo



Una mezcla del ácido 3-(4-bifenilil)-propiónico (5 gramos, 22.10 milimoles), y $SOCl_2$ (4.03 mililitros, 55.2 milimoles) se pone a reflujo bajo nitrógeno a 85°C durante 1.5 horas. La mezcla de reacción se concentra bajo presión reducida, para dar el cloruro de 3-(bifenil-4-il)-propanoílo (5.46 gramos). El material se utiliza en el siguiente paso sin mayor purificación.

Intermediario 14: Trifluoro-acetato de etil-éster del ácido (2R,4R)-4-amino-2-metil-pentanoico



A una solución agitada del etil-éster del ácido 2-(trifenil-

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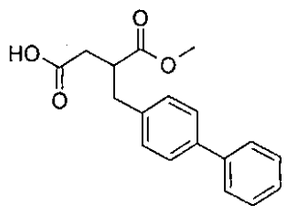
fosfaniliden)-propiónico (3.11 gramos, 8.57 milimoles) en cloruro de metileno (20 mililitros), se le agrega una solución de 3,3-dimetil-N-((R)-1-metil-2-oxo-etil)-butiramida (J. Med. Chem. **41**, 6 (1998) (1.35 gramos, 7.79 milimoles) en cloruro de metileno (20 mililitros), y la mezcla se agita a temperatura ambiente durante 2 horas. El solvente se remueve bajo presión reducida, y el residuo se purifica mediante cromatografía en columna utilizando un gradiente del 10 al 50 por ciento de heptano/EtOAc, para dar el etil-éster del ácido (E)-(R)-4-terbutoxi-carbonil-amino-2-metil-pent-2-enoico. ^{1}H-RMN (400 MHz, $CDCl_3$); δ ppm 1.22 (d, J=6.44 Hz, 3H), 1.30 (t, 3H), 1.43 (s, 9H), 1.91 (s, 3H), 4.19 (q, 2H), 6.51 (d, amplia, J=7.45 Hz, 1H).

En seguida, una solución del etil-éster del ácido (E)-(R)-4-terbutoxi-carbonil-amino-2-metil-pent-2-enoico (1.83 gramos, 7.11 milimoles) en acetato de etilo (75 mililitros) se hidrogena sobre Pt/C al 10 por ciento (183 miligramos) a 1 atmósfera durante 18 horas. El catalizador se filtra a través de Celite, y el solvente se remueve bajo presión reducida. El residuo se purifica mediante HPLC quiral para proporcionar el etil-éster del ácido (2R,4R)-4-terbutoxi-carbonil-amino-2-metil-pentanoico, ^{1}H-RMN (400 MHz, $CDCl_3$); δ ppm 1.13 (t, 3H), 1.18 (m, 3H), 1.26 (t, 3H), 1.43 (s, 9H), 1.81 (s, 1H), 2.50 (m, 1H), 3.72 (m amplia, 1H), 4.14 (m, 2H), 4.33 (m amplia, 1H).

En seguida, el etil-éster del ácido (2R,4R)-4-terbutoxi-carbonil-amino-2-metil-pentanoico (142 miligramos, 0.548 milimoles) se agrega al ácido trifluoro-acético (5 mililitros). Después de 10 minutos, el solvente se remueve bajo presión reducida. Se agrega

cloruro de metileno, y el solvente se remueve bajo presión reducida, para dar el trifluoro-acetato de etil-éster del ácido (2R,4R)-4-amino-2-metil-pentanoico. Este material se utiliza directamente en la siguiente reacción de acoplamiento.

Intermediario 15: 1-metil-éster del ácido 2-bifenil-4-il-metil-succínico



A una solución del metil-éster del ácido (trifenil-fosfaniliden)-acético (2.26 gramos, 6.77 milimoles) en cloruro de metileno (25 mililitros), se le agrega bromo-acetato de terbutilo (1.32 gramos, 6.77 milimoles), y la mezcla se agita a temperatura ambiente durante 48 horas. El solvente se remueve bajo presión reducida, y el residuo se purifica mediante cromatografía en columna utilizando un gradiente del 80 al 100 por ciento de heptano/EtOAc, para proporcionar el 1-metil-éster de 4-terbutil-éster del ácido 2-(trifenil-fosfaniliden)-succínico. MS 449.3 (M+1).

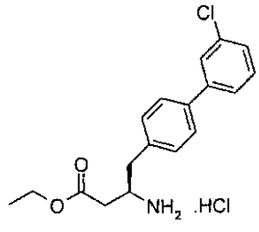
En seguida, una mezcla del 1-metil-éster de 4-terbutil-éster del ácido 2-(trifenil-fosfaniliden)-succínico (700 miligramos, 1.561 milimoles), y bifenil-4-carboxaldehído (278 miligramos, 1.419 milimoles) en tolueno (20 mililitros), se pone a reflujo durante 4 días. El solvente se remueve bajo presión reducida, y el residuo se purifica mediante cromatografía en columna utilizando un gradiente del 0 al

30 por ciento de heptano/EtOAc, para dar el 1-metil-éster de 4-terbutil-éster del ácido 2-[1-bifenil-4-il-met-(Z)-ilíden]-succínico como un aceite, ^{1}H-RMN (400 MHz, $CDCl_3$); δ ppm 1.47 (s, 9H), 3.52 (s, 2H), 3.84 (s, 3H), 7.37 (t, 1H), 7.46 (t, 4H), 7.62 (t, 4H), 7.89 (s, 1H).

Una solución del 1-metil-éster de 4-terbutil-éster del ácido 2-[1-bifenil-4-il-met-(Z)-ilíden]-succínico (410 miligramos, 1.163 milimoles) en acetato de etilo (20 mililitros) se hidrogena sobre Pt/C (40 miligramos) a 1 atmósfera durante 18 horas. El catalizador se filtra a través de Celite, y el solvente se remueve bajo presión reducida, para dar el 1-metil-éster de 4-terbutil-éster del ácido 2-bifenil-4-il-metil-succínico. Los enantiómeros se separan mediante HPLC quiral.

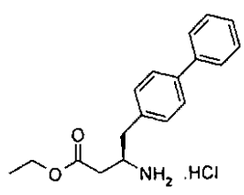
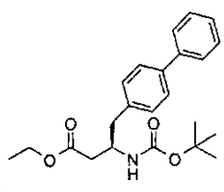
En seguida, el 1-metil-éster de 4-terbutil-éster del ácido 2-bifenil-4-il-metil-succínico (160 miligramos, 0.451 milimoles) se agrega al ácido trifluoro-acético (5 mililitros). Después de 10 minutos, el solvente se remueve bajo presión reducida. Se agrega cloruro de metileno, y el solvente se remueve bajo presión reducida, para dar el 1-metil-éster del ácido 2-bifenil-4-il-metil-succínico. Este material se utiliza directamente en la siguiente reacción de acoplamiento.

Intermediario 16-1: Síntesis de clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-etilo

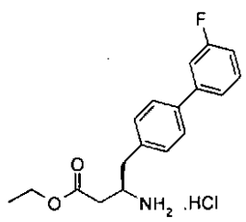
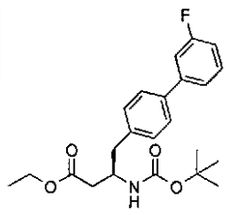
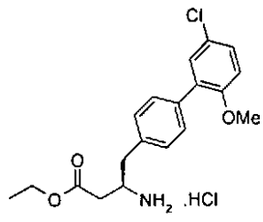
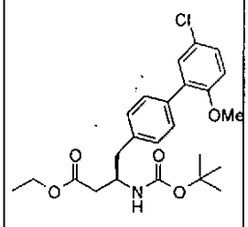


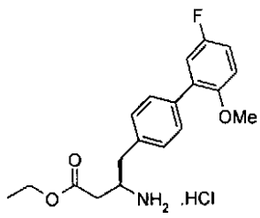
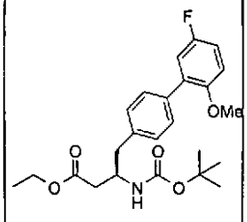
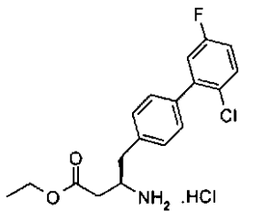
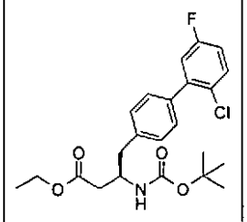
Al 3-(terbutoxi-carbonil-amino)-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-etilo (3.33 gramos, 7.97 milimoles), se le agrega una solución de HCl 4M en 1,4-dioxano (19.9 mililitros, 18.0 milimoles) a temperatura ambiente. Después de agitar durante 0.5 horas, la mezcla de reacción se concentra bajo presión reducida, para dar el clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-etilo (2.90 gramos). HPLC - tiempo de retención = 0.70 minutos (condición B); MS (m+1) = 318.26; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.19 – 1.24 (m, 3 H) 2.73 – 2.78 (m, 1 H) 2.84 – 2.91 (m, 1 H) 3.05 – 3.11 (m, 1 H) 3.50 – 3.54 (m, 1 H) 3.92 (br s, 1 H) 4.14 – 4.17 (m, 2 H) 7.29 – 7.53 (m, 8 H) 8.73 (br. s., 3 H).

Los siguientes intermediarios se preparan empleando un procedimiento similar al que se describe para el intermediario 16-1:

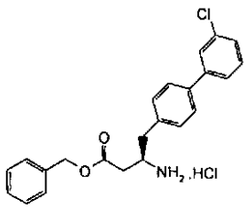
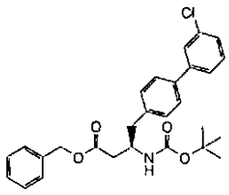
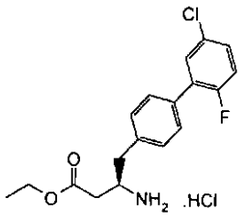
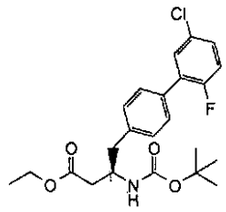
Interme-diario #	**Producto**	**Material de partida**	**Condi-ción**	**HPLC-RT (condición)**	**MS (M+1)**
Interme-diario 16-2	 clorhidrato de 3-amino-4-(bifenil-4-il)-butanoato de (R)-etilo	 Intermediario 2	4M HCl/1,4-dioxano	0.89 minutos. (B)	284.1

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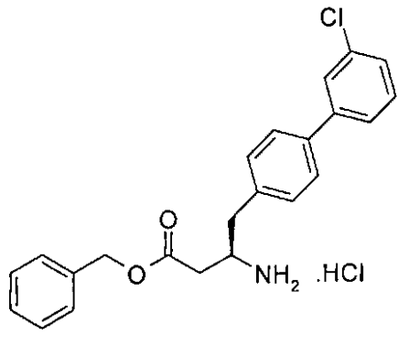
Intermediario #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
Intermediario 16-3	 clorhidrato de 3-amino-4-(3'-fluoro-bifenil-4-il)-butanoato de (R)-etilo	 Intermediario 2-2	4M HCl/1,4-dioxano	0.94 minutos. (B)	302.1
Intermediario 16-4	 clorhidrato de 3-amino-4-(5'-cloro-2'-metoxi-bifenil-4-il)-butanoato de (R)-etilo	 Intermediario 2-3	4M HCl/1,4-dioxano	0.94 minutos. (B)	348.2

Intermediario #	Producto	Material de partida	Condición	HPLC-RT (condición)	MS (M+1)
Intermediario 16-5	 clorhidrato de 3-amino-4-(5'-fluoro-2'-metoxi-bifenil-4-il)-butanoato de (R)-etilo	 Intermediario 2-4	4M HCl/1,4-dioxano	1.38 minutos. (A)	332.2
Intermediario 16-6	 clorhidrato de 3-amino-4-(2'-cloro-5'-fluoro-bifenil-4-il)-butanoato de (*R*)-etilo	 Intermediario 2-5	4M HCl/1,4-dioxano	0.93 minutos. (B)	336.1

325

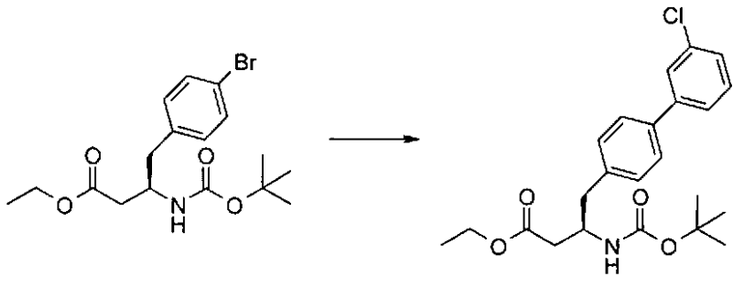
Interme-diario #	Producto	Material de partida	Condi-ción	HPLC-RT (condición)	MS (M+1)
Interme-diario 16-7	 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo	 Intermediario 17-2	4M HCl/1,4-dioxano	1.20 minutos. (B)	380.2
Interme-diario 16-8	 3-amino-4-(5'-cloro-2'-fluoro-bifenil-4-il)-butanoato de (R)-etilo	 Intermediario 2-6	4M HCl/1,4-dioxano	0.88 minutos. (B)	336.1

Intermediario 16-7: Clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo



Al 3-(terbutoxi-carbonilamino)-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo (3.561 gramos, 7.42 milimoles), se le agrega una solución de HCl 4M en 1,4-dioxano (18.55 mililitros, 74.2 milimoles) a temperatura ambiente. Después de agitar durante 4 horas, la mezcla de reacción se concentra bajo presión reducida, para dar el clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo (3.11 gramos). HPLC - tiempo de retención = 1.07 minutos (condición B); MS (m+1) = 380.1; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 2.81 (A de ABX, J_{ab} = 17.4 Hz, J_{ax} = 4.5 Hz, 1 H) 2.93 (B de ABX, J_{ab} = 17.4 Hz, J_{bx} = 7.6 Hz, 1 H) 3.03 – 3.09 (m, 1 H) 3.50 (dd, J = 4.9 y 13.5 Hz, 1 H) 3.98 (br s, 1 H) 5.09 (s, 2 H) 7.24 – 7.22 (m, 9 H) 7.35 – 7.38 (m, 1 H) 7.42 (d, J = 8.1 Hz, 2 H) 7.48 – 7.49 (m, 1 H) 8.78 (br s, 3 H).

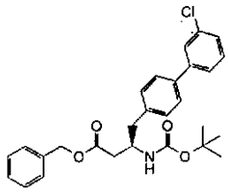
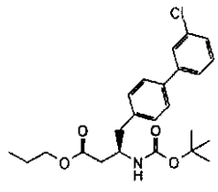
Intermediario 17-1: Síntesis de 3-(terbutoxi-carbonil-amino)-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-etilo



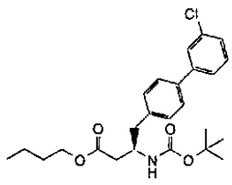
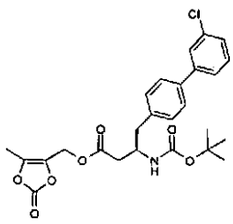
Una mezcla del 4-(4-bromo-fenil)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-etilo (4.89 gramos, 12.66 milimoles), ácido 3-cloro-fenil-borónico (2.97 gramos, 18.99 milimoles), $Pd(PPh_3)_4$ (1.463 gramos, 1.266 milimoles), y Na_2CO_3 acuoso 2 M (12.66 mililitros, 25.3 milimoles) en 1,2-dimetoxi-etano (100 mililitros) se deja agitándose a 95°C bajo nitrógeno durante 3 horas. La mezcla de reacción se enfría a temperatura ambiente, y se apaga con salmuera. Las dos fases se separan. La mezcla se extrae dos veces con acetato de etilo a partir de la capa acuosa. La capa orgánica combinada se lava con salmuera, se seca sobre $MgSO_4$, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea en gel de sílice (heptano/EtOAc = 100:0 a 70:30), para dar el 3-(terbutoxi-carbonil-amino)-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-etilo (3.33 gramos); HPLC - tiempo de retención = 1.44 minutos (condición B); MS (ES+) = 318.26 (m-BOC+2; 100 por ciento); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, *J* = 7.2 Hz, 3 H) 1.41 (s, 9 H) 2.47 (A de ABX, J_{ab} = 15.8 Hz, J_{ax} = 5.9 Hz, 1 H) 2.52 (B de ABX, J_{ab} = 15.8 Hz, J_{bx} = 5.4 Hz, 1 H) 2.83 – 2.89 (m, 1 H) 2.95 – 3.00 (m, 1 H) 4.17 (q, *J* = 7.2 Hz, 2 H) 4.18 (br s, 1 H) 5.07 (br s, 1

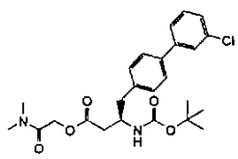
H) 7.26 – 7.37 (m, 4 H) 7.43 – 7.51 (m, 3 H) 7.55 (br t, *J* = 1.8 Hz, 1 H).

Los siguientes intermediarios se preparan empleando un procedimiento similar al que se describe para el intermediario 17-1:

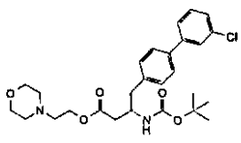
Interme-diario #	Producto	Condición	HPLC-RT (condición)	MS (ES+; 100%)
Interme-diario 17-2	 3-(terbutoxi-carbonil-amino)-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo	$Pd(PPh_3)_4$, ácido 3-cloro-fenil-borónico, Na_2CO_3 acuoso 2M, tolueno, 95°C	1.74 minutos. (B)	380.2 (m-BOC+2)
Interme-diario 17-3	 propil-éster del ácido (R)-3-terbutoxi-carbonil-amino-	$Pd(PPh_3)_4$, ácido 3-cloro-fenil-borónico, Na_2CO_3 acuoso 2M, tolueno, 95°C	1.66 minutos. (B)	432 (m+1)

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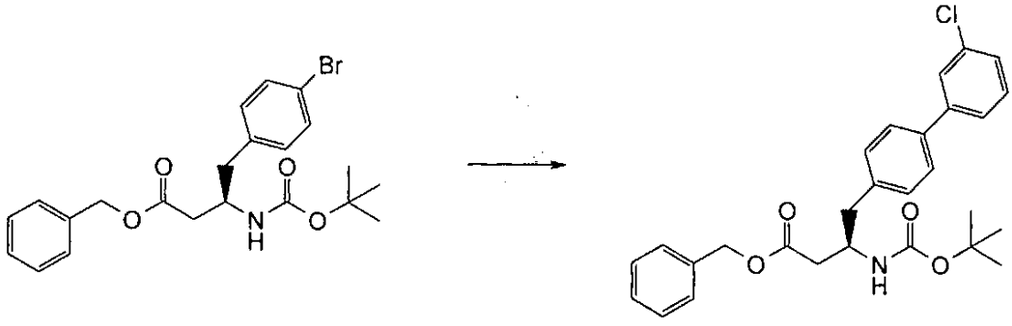
Interme-diario #	Producto	Condición	HPLC-RT (condición)	MS (ES+; 100%)
	4-(3'-cloro-bifenil-4-il)-butírico			
Interme-diario 17-4	 butil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-butírico	$Pd(PPh_3)_4$, ácido 3-cloro-fenil-borónico, Na_2CO_3 acuoso 2M, tolueno, 95°C	1.73 minutos. (B)	446 (m+1)
Interme-diario 17-5	 5-metil-2-oxo-[1,3]-dioxol-4-	$Pd(OAc)_2$, diciclohexil-(2',6'-dimetoxi-bifenil-2-il)-fosfano, ácido 3-cloro-fenil-borónico,	1.53 minutos. (B)	502 (m+1)

Interme-diario #	Producto	Condición	HPLC-RT (condición)	MS (ES+; 100%)
	il-metil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-butírico	K_3PO_4, tolueno, 95°C		
Interme-diario 17-6	 dimetil-carbamoil-metil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-butírico	$Pd(PPh_3)_4$, ácido 3-cloro-fenil-borónico, K_3PO_4, N,N-dimetil-formamida, 95°C	1.51 minutos. (B)	475 (m+1)

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Interme-diario #	Producto	Condición	HPLC-RT (condición)	MS (ES+; 100%)
Interme-diario 17-7	 2-morfolin-4-il-etil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-butírico	$Pd(PPh_3)_4$, ácido 3-cloro-fenil-borónico, K_3PO_4, N,N-dimetil-formamida, 95°C	1.51 minutos. (B)	503 (m+1)

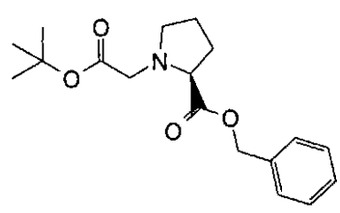
Intermediario 17-2: 3-(terbutoxi-carbonil-amino)-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo



Una suspensión de 4-(4-bromo-fenil)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-bencilo (2.00 gramos, 4.46 milimoles), ácido

3-cloro-fenil-borónico (1.046 gramos, 6.69 milimoles), $Pd(PPh_3)_4$ (0.515 gramos, 0.446 milimoles), y Na_2CO_3 acuoso (4.46 mililitros, 8.92 milimoles) en tolueno (30 mililitros), se deja agitándose bajo nitrógeno a 95°C durante 19 horas. La mezcla de reacción se enfría a temperatura ambiente, y se diluye con salmuera y EtOAc. Los productos se extraen dos veces con EtOAc, se lavan con salmuera, se secan sobre $MgSO_4$, se filtran, y se concentran. El residuo se purifica mediante cromatografía en columna por evaporación instantánea sobre 90 gramos de gel de sílice (eluyente: heptano/EtOAc = 100:0 a 65:35), para dar el 3-(terbutoxi-carbonil-amino)-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo (1.03 gramos); HPLC - tiempo de retención = 1.74 minutos (condición B); MS (ES+) = 380.2 (m-BOC+2; 100 por ciento); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.40 (s, 9 H) 2.52 (A de ABX, J_{ab} = 15.9 Hz, J_{ax} = 5.8 Hz, 1 H) 2.58 (B de ABX, J_{ab} = 15.9 Hz, J_{bx} = 5.6 Hz, 1 H) 2.81 – 2.98 (m, 2 H) 4.19 (br s, 1 H) 5.07 (br d, 1 H) 5.12 (A de AB, J = 12.3 Hz, 1 H) 5.17 (A de AB, J = 12.3 Hz, 1 H) 7.20 – 7.22 (m, 2 H) 7.28 – 7.39 (m, 7 H) 7.42 – 7.47 (m, 3 H) 7.53 – 7.54 (m, 1 H).

Intermediario 18: Síntesis de 1-(2-terbutoxi-2-oxo-etil)-pirrolidin-2-carboxilato de (S)-bencilo

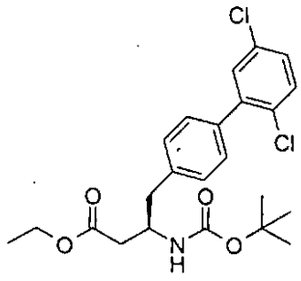


A una suspensión del clorhidrato de pirrolidin-2-carboxilato de

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(S)-bencilo (700 miligramos, 2.90 milimoles), y K_2CO_3 (1201 miligramos, 8.69 milimoles) en N,N-dimetil-formamida (7 mililitros), se le agrega bromo-acetato de terbutilo (0.535 mililitros, 3.62 milimoles). Después de agitar durante 71 horas, a la mezcla de reacción se le agrega K_2CO_3 acuoso (1.5 gramos de K_2CO_3 / 40 mililitros de H_2O). Los productos se extraen con EtOAc. La capa orgánica se lava dos veces con agua y una vez con salmuera, se seca sobre K_2CO_3, se filtra, y se concentra, para dar el 1-(2-terbutoxi-2-oxo-etil)-pirrolidin-2-carboxilato de (S)-bencilo (458 miligramos); HPLC - tiempo de retención = 1.38 minutos (condición D); MS (m+1) = 320.2; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.44 (s, 9 H) 1.81 – 2.03 (m, 3 H) 2.13 – 2.14 (m, 1 H) 2.82 – 2.88 (m, 1 H) 3.13 – 3.17 (m, 1 H) 3.46 (A de AB, *J* = 17.3 Hz, 1 H) 3.49 (B de AB, *J* = 17.3 Hz, 1 H) 3.73 (dd, *J* = 8.8 y 4.8 Hz, 1 H) 5.15 (A de AB, *J* = 12.4 Hz, 1 H) 5.17 (B de AB, *J* = 12.4 Hz, 1 H) 7.29 – 7.38 (m, 5 H).

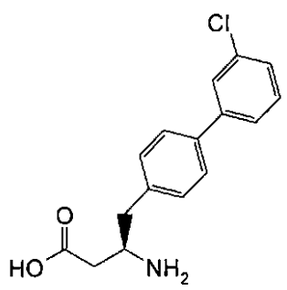
Intermediario 19: Síntesis de 3-(terbutoxi-carbonil-amino)-4-(2',5'-dicloro-bifenil-4-il)-butanoato de (R)-etilo



Una mezcla del 4-(4-bromo-fenil)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-etilo (1.005 gramos, 2.60 milimoles), ácido 2,5-

dicloro-fenil-borónico (0.745 gramos, 3.90 milimoles), $Pd(PPh_3)_4$ (0.301 gramos, 0.260 milimoles), y Na_2CO_3 acuoso 2 M (2.60 mililitros, 5.20 milimoles) en 1,2-dimetoxi-etano (20 mililitros), se deja agitándose a 95°C bajo nitrógeno durante 3 horas. La mezcla de reacción se enfría a temperatura ambiente, y se diluye con salmuera. Las dos fases se separan. Los productos se extraen dos veces con acetato de etilo (100 mililitros, 2 veces) a partir de la capa acuosa. La capa orgánica combinada se lava con salmuera, se seca sobre $MgSO_4$, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea en gel de sílice (heptano/EtOAc = 100:0 a 70:30), para dar el 3-(terbutoxi-carbonil-amino)-4-(2',5'-dicloro-bifenil-4-il)-butanoato de (R)-etilo (1.09 gramos); HPLC - tiempo de retención = 1.50 minutos (condición B); MS (ES+) = 352.00 (m-BOC+2; 100 por ciento); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, *J*= 7.1 Hz, 3 H) 1.41 (s, 9 H) 2.45 – 2.58 (m, 2 H) 2.85 – 3.00 (m, 2 H) 4.17 (t, *J* = 7.1 Hz, 2 H) 4.20 (br s, 1 H) 5.06 – 5.08 (m, 1 H) 7.23 – 7.28 (m, 3 H) 7.31 – 7.40 (m, 4 H).

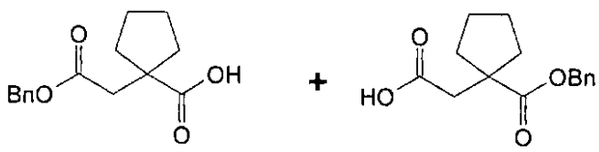
Intermediario 20: Síntesis de clorhidrato de ácido (R)-3-amino-4-(3'-cloro-bifenil-4-il)-butanoico



Una solución del 3-(terbutoxi-carbonil-amino)-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-bencilo (152 miligramos, 0.317 milimoles), y NaOH 1 M acuoso (1.583 mililitros, 1.583 milimoles) en un solvente mixto de metanol (0.3 mililitros) y tetrahidrofurano (3 mililitros), se deja agitándose durante 2 horas. La reacción se apaga con HCl acuoso 1M (2.5 mililitros). Los productos se extraen con EtOAc. La capa orgánica se seca sobre Na_2SO_4, se filtra, y se concentra, para dar el producto crudo.

Al producto crudo se le agrega una solución de HCl 4M en 1,4-dioxano (1.583 mililitros, 6.33 milimoles). Después de agitar durante 1 hora, el sólido precipitado se recolecta y se seca bajo presión reducida, para dar el clorhidrato de ácido (R)-3-amino-4-(3'-cloro-bifenil-4-il)-butanoico (60.2 miligramos) como un sólido blanco; HPLC - tiempo de retención = 0.52 minutos (condición B); MS (m+1) = 290.22; ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.58 - 2.74 (m, 2 H) 2.99 – 3.11 (m, 2 H) 3.80 – 3.85 (m, 1 H) 7.34 - 7.45 (m, 4 H) 7.54 - 7.57 (m, 1 H) 7.62 - 7.65 (m, 3 H).

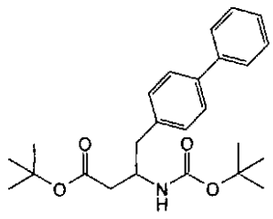
Intermediario 21: Síntesis de una mezcla de ácido 1-(2-(benciloxi)-2-oxo-etil)-ciclopentan-carboxílico y ácido 2-(1-(benciloxi-carbonil)-ciclopentil)-acético



Una solución de la 2-oxaespiro-[4.4]-nonano-1,3-diona (3 gramos, 19.46 milimoles), y alcohol bencílico (2.023 mililitros, 19.46

milimoles) en tolueno (2 mililitros), se deja agitándose a 100°C durante 19 horas. La mezcla de reacción se enfría a temperatura ambiente, y se concentra, para dar una mezcla de 6:1 del ácido 1-(2-(benciloxi)-2-oxo-etil)-ciclopentan-carboxílico y el ácido 2-(1-(benciloxi-carbonil)-ciclopentil)-acético (4.89 gramos); ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.60 - 1.78 (m, 6 H) 2.19 – 2.24 (m, 2 H) 2.75 (s, 2 H) 5.11 (s, 2 H, isómero mayor) 5.13 (s, 2 H, isómero menor) 7.30 – 7.37 (m, 5 H).

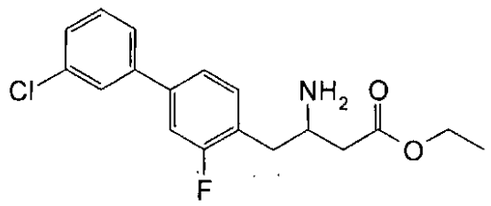
Intermediario 22: Síntesis de 4-(bifenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoato de terbutilo



Una solución del ácido 4-(bifenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoico (250 miligramos, 0.703 milimoles), tBuOH (0.135 mililitros, 1.407 milimoles), EDCI (270 miligramos, 1.407 milimoles), y 4-dimetil-amino-piridina (86.0 miligramos, 0.704 milimoles) en dicloro-metano (7 mililitros), se deja agitándose a temperatura ambiente bajo nitrógeno durante 62 horas. La reacción se apaga con agua, y la capa orgánica se separa y se concentra. El residuo se purifica mediante cromatografía en columna por evaporación instantánea sobre gel de sílice, para dar el 4-(bifenil-4-il)-3-(terbutoxi-carbonil-amino)-butanoato de terbutilo (110 miligramos); HPLC - tiempo de retención = 1.77 minutos (condición B); MS (ES+)

= 412.1 (m+1) 300.0 (m-tBux2+3; 100 por ciento); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.41 (s, 9 H) 1.47 (s, 9 H) 2.36 (A de ABX, J_{ab} = 15.5 Hz, J_{ax} = 6.2 Hz, 1 H) 2.44 (B de ABX, J_{ab} = 15.5 Hz, J_{bx} = 5.6 Hz) 2.82 – 2.94 (m, 2 H) 4.11 – 4.17 (m, 1 H) 5.08 – 5.10 (m, 1 H) 7.25 - 7.34 (m, 3H) 7.41 – 7.44 (m, 2 H) 7.51-7.58 (m, 4 H).

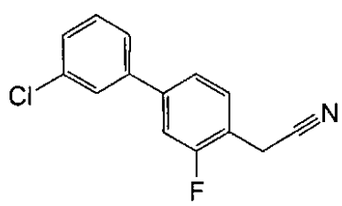
Intermediario 23: Síntesis de 3-amino-4-(3'-cloro-3-fluoro-bifenil-4-il)-butanoato de etilo



Una suspensión de zinc (479 miligramos, 7.33 milimoles), y 1,2-dibromo-etano (0.032 mililitros, 0.366 milimoles) en tetrahidrofurano (8 mililitros), se calienta a 70°C bajo nitrógeno, y entonces se agregan unas cuantas gotas de bromo-acetato de etilo. Después de agitar durante 20 minutos, se agrega una solución de 2-(3'-cloro-3-fluoro-bifenil-4-il)-acetonitrilo (300 miligramos, 1.221 milimoles) en tetrahidrofurano (2 mililitros) en una porción. El bromo-acetato restante se agrega por goteo durante 50 minutos (cantidad total de bromo-acetato de etilo: 4.88 milimoles). Después de agitar durante 15 minutos a la misma temperatura, la mezcla de reacción se enfría a temperatura ambiente. A la mezcla de reacción, se le agregan triacetoxi-borohidruro de sodio (2588 miligramos, 12.22 milimoles) y AcOH (8 mililitros). La mezcla de reacción se deja agitándose durante 13 horas, y se concentra, para dar el producto

crudo. El producto crudo se diluye con EtOAc, y se agrega Na_2CO_3 acuoso 2M, para tener un pH de 10. Los productos se extraen con EtOAc. La capa orgánica se seca sobre K_2CO_3, se filtra, y se concentra, para dar el producto crudo. El residuo resultante se purifica mediante HPLC de preparación utilizando un gradiente del 20 por ciento de MeCN/agua (0.1 por ciento NH_4OH) al 100 por ciento de MeCN, para dar el 3-amino-4-(3'-cloro-3-fluoro-bifenil-4-il)-butanoato de etilo (148 miligramos) como un aceite color naranja; HPLC - tiempo de retención = 0.85 minutos (condición B); MS (m+1) = 336.13; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.27 (t, *J* = 7.1 Hz, 3 H) 2.36 (A de ABX, J_{ab} = 15.9 Hz, J_{ax} = 8.8 Hz, 1 H) 2.52 (B de ABX, J_{ab} = 15.9 Hz, J_{bx} = 4.0 Hz, 1 H) 2.71 – 2.76 (m, 1 H) 2.82 – 2.87 (m, 1 H) 3.51 – 3.57 (m, 1 H) 4.15 (d, *J* = 7.1 Hz, 2 H) 7.24 – 7.39 (m, 5 H) 7.42 – 7.44 (m, 1 H) 7.54 – 7.55 (m, 1 H).

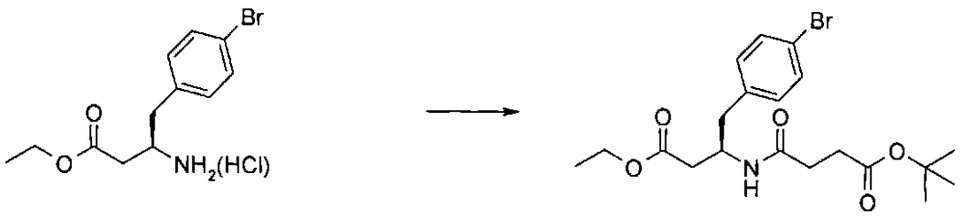
Intermediario 24: Síntesis de 2-(3'-cloro-3-fluoro-bifenil-4-il)-acetonitrilo



Una suspensión de cianuro de 4-bromo-2-fluoro-bencilo (3.50 gramos, 16.35 milimoles), ácido 3-cloro-bencen-borónico (2.68 gramos, 17.17 milimoles), $Pd(OAc)_2$ (0.110 gramos, 0.491 milimoles), K_2CO_3 (5.65 gramos, 40.9 milimoles), y bromuro de tetrabutil-amonio (5.80 gramos, 17.99 milimoles) en agua (14 mililitros), se deja

agitándose bajo nitrógeno a 70°C durante 1 hora. La mezcla de reacción se enfría a temperatura ambiente, y se diluye con EtOAc. Las dos fases se separan. La capa orgánica se lava con salmuera, se seca sobre $MgSO_4$, se filtra, y se concentra. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea en gel de sílice (heptano/EtOAc = 100:0 a 70:30), para dar el 2-(3'-cloro-3-fluoro-bifenil-4-il)-acetonitrilo (3.52 gramos); HPLC - tiempo de retención = 1.17 minutos (condición B); ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 3.81 (s, 2 H) 7.29 – 7.45 (m, 5 H) 7.50 – 7.55 (m, 2 H).

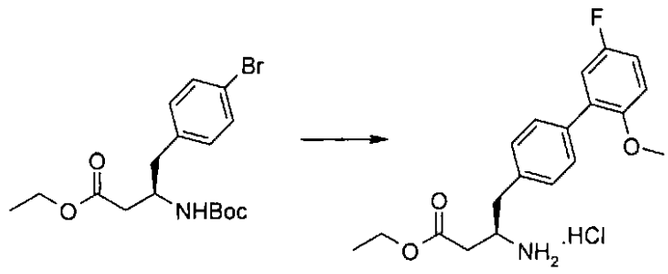
Intermediario 25: 4-(1-(4-bromo-fenil)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoato de (R)-terbutilo



A una solución del ácido 4-terbutoxi-4-oxo-butanoico (2.38 gramos, 13.64 milimoles) en N,N-dimetil-formamida (30 mililitros), y dicloro-metano (30 mililitros), se le agrega clorhidrato de 3-amino-4-(4-bromo-fenil)-butanoato de (R)-etilo (4 gramos, 12.4 milimoles), HATU (5.19 gramos, 13.64 milimoles), y trietil-amina (6.91 mililitros, 49.6 milimoles). Después de agitar a temperatura ambiente durante 2 horas, la reacción se apaga con H_2O, y el producto crudo se diluye

con EtOAc, la capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida, para dar el 4-(1-(4-bromo-fenil)-4-etoxi-4-oxo-butan-2-il-amino)-4-oxo-butanoato de (R)-terbutilo (4.0 gramos). HPLC - tiempo de retención = 1.70 minutos (condición A); MS (m+1) = 444.1.

Intermediario 26: Sal de clorhidrato de etil-éster del ácido (R)-3-amino-4-(5'-fluoro-2'-metoxi-bifenil-4-il)-butírico

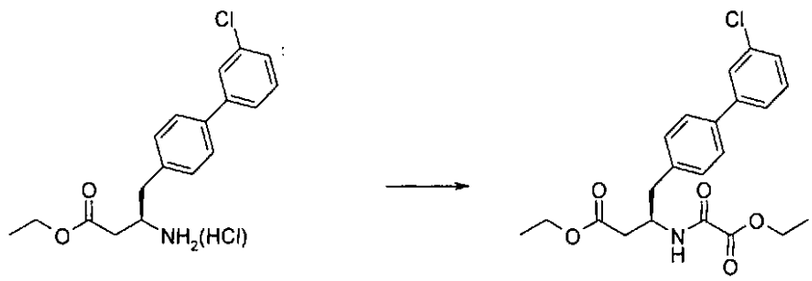


A una solución del 4-(4-bromo-fenil)-3-(terbutoxi-carbonil-amino)-butanoato de (R)-etilo, (3.12 gramos, 8.08 milimoles), y ácido 5-fluoro-2-metoxi-fenil-borónico (2.2 gramos, 12.93 milimoles) en tolueno (52 mililitros), y se le agregan el aducto de $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.66 gramos, 0.81 milimoles), y Na_2CO_3 acuoso 2M (8.1 mililitros, 16.16 milimoles). Después de agitar a 95°C bajo nitrógeno durante 4 horas, la solución se enfría a temperatura ambiente, y entonces se apaga con agua helada. El producto crudo se diluye con acetato de etilo. La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante

cromatografía en columna por evaporación instantánea sobre gel de sílice (eluyente: heptano/EtOAc = 100:0 a 50:50), para dar el 3-(terbutoxi-carbonil-amino)-4-(5'-fluoro-2'-metoxi-bifenil-4-il)-butanoato de (R)-etilo (2.86 gramos). HPLC - tiempo de retención = 1.80 minutos (condición A); MS (m+1) = 432.2; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.31 (t, *J*=7.1 Hz, 3 H) 1.45 (s, 9 H) 2.45 - 2.65 (m, 2 H) 2.83 - 2.94 (m, 1 H) 2.94 - 3.09 (m, 1 H) 3.80 (s, 3 H) 4.20 (q, *J*=7.2 Hz, 2 H) 4.24 - 4.33 (m, 1 H) 5.11 (br. s., 1 H) 6.90 - 6.96 (m, 1 H) 7.00 (dd, *J*=7.8, 3.3 Hz, 1 H) 7.06 (dd, *J*=9.2, 3.2 Hz, 1 H) 7.27 (d, *J*=7.8 Hz, 2 H) 7.49 (d, *J*=7.8 Hz, 2 H)

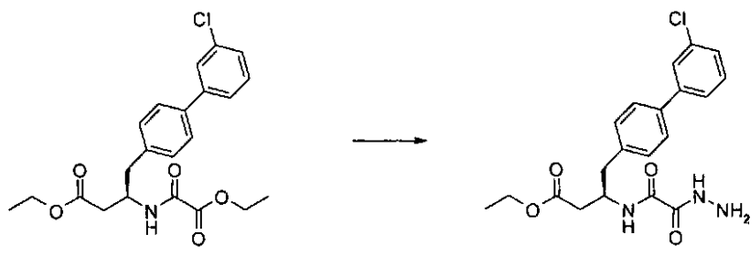
Una solución del 3-(terbutoxi-carbonil-amino)-4-(5'-fluoro-2'-metoxi-bifenil-4-il)-butanoato de (R)-etilo, (2.86 gramos, 6.62 milimoles) en HCl 4M en 1,4-dioxano (33.1 mililitros, 132 milimoles), se agita a temperatura ambiente. Después de agitar durante 1 hora, la mezcla de reacción se concentra bajo presión reducida, para dar la sal de clorhidrato de 3-amino-4-(5'-fluoro-2'-metoxi-bifenil-4-il)-butanoato de (R)-etilo (2.44 gramos). HPLC - tiempo de retención = 1.46 minutos (condición A); MS (m+1) = 332.3; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.15 (t, *J*=6.4 Hz, 3 H) 2.66 - 2.77 (m, 1 H) 2.78 - 2.91 (m, 1 H) 2.94 - 3.10 (m, 1 H) 3.42 - 3.53 (m, 1 H) 3.67 (s, 3 H) 3.83 - 3.96 (m, 1 H) 4.07 (q, *J*=6.8 Hz, 2 H) 6.77 - 6.84 (m, 1 H) 6.87 - 6.96 (m, 2 H) 7.23 (d, *J*=7.1 Hz, 2 H) 7.38 (d, *J*=7.1 Hz, 2 H) 8.64 (br. s., 2 H)

Intermediario 27: 4-(3'-cloro-bifenil-4-il)-3-(2-etoxi-2-oxo-acetamido)-butanoato de (R)-etilo



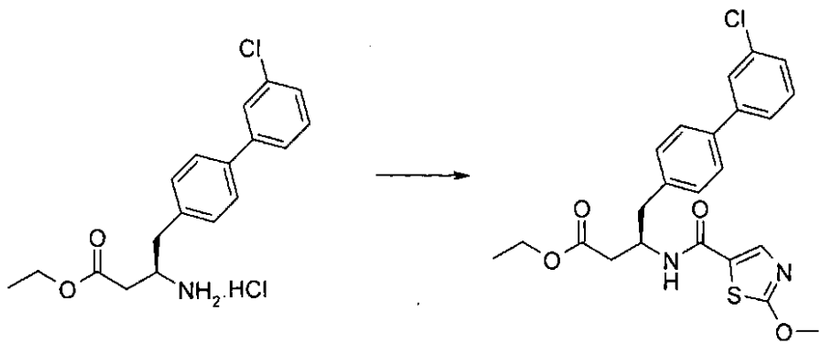
A una solución del clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-etilo (500 miligramos, 1.57 milimoles) en N,N-dimetil-formamida (11 mililitros), se le agrega trietil-amina (0.23 mililitros, 1.65 milimoles), y 2-cloro-2-oxo-acetato de etilo (0.18 mililitros, 1.57 milimoles) a temperatura ambiente. Después de agitar durante 1 hora a temperatura ambiente, la reacción se apaga con H_2O, y el producto crudo se diluye con EtOAc. La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea sobre gel de sílice (eluyente: heptano/EtOAc = 70:30 a 50:50), para dar el 4-(3'-cloro-bifenil-4-il)-3-(2-etoxi-2-oxo-acetamido)-butanoato de (R)-etilo (550 miligramos). HPLC - tiempo de retención = 1.88 minutos (condición A); MS (m+1) = 418.3

Intermediario 28: 4-(3'-cloro-bifenil-4-il)-3-(2-hidrazinil-2-oxo-acetamido)-butanoato de (R)-etilo



A una solución del 4-(3'-cloro-bifenil-4-il)-3-(2-etoxi-2-oxo-acetamido)-butanoato de (R)-etilo (450 miligramos, 1.08 milimoles) en metanol (24 mililitros), se le agrega una solución de hidrazina al 50 por ciento en peso (0.068 mililitros, 1.08 milimoles) en metanol (10 mililitros) a -20°C. Después de agitar durante 18 horas a temperatura ambiente, la mezcla de reacción se concentra bajo presión reducida, para dar el 4-(3'-cloro-bifenil-4-il)-3-(2-hidrazinil-2-oxo-acetamido)-butanoato de (R)-etilo (412 miligramos). HPLC - tiempo de retención = 1.76 minutos (condición A); MS (m+1) = 404.1

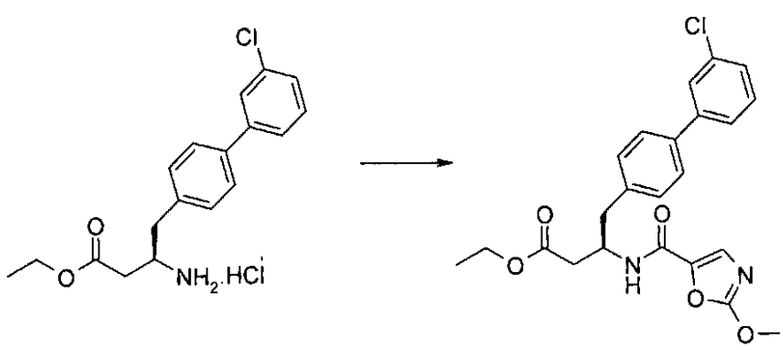
Intermediario 29: 4-(3'-cloro-bifenil-4-il)-3-(2-metoxi-tiazol-5-carboxamido)-butanoato de (R)-etilo



A una solución del ácido 2-metoxi-tiazol-5-carboxílico (80 miligramos, 0.50 milimoles), y clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-etilo (160 miligramos, 0.45 milimoles) en N,N-dimetil-formamida (5 mililitros), se le agregan HATU (207 miligramos, 0.55 milimoles), y trietil-amina (276 miligramos, 2.73 milimoles). El producto crudo se agita a temperatura ambiente durante 2 horas. El producto crudo se neutraliza con HCl 1N y se diluye en agua y EtOAc. La capa orgánica se lava con salmuera, se

seca sobre $MgSO_4$, se filtra, y se concentra. El producto crudo se purifica por medio de cromatografía por evaporación instantánea utilizando desde el 30 por ciento de EtOAc/heptano hasta el 70 por ciento de EtOAc/heptano, para dar el 4-(3'-cloro-bifenil-4-il)-3-(2-metoxi-tiazol-5-carboxamido)-butanoato de (R)-etilo (170 miligramos). HPLC - tiempo de retención = 1.97 minutos (condición D); MS (m+1) = 459.1. ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.29 (t, *J*=7.1 Hz, 3 H) 2.49 - 2.69 (m, 2 H) 2.93 (dd, *J*=13.6, 8.1 Hz, 1 H) 3.10 (dd, *J*=13.5, 6.2 Hz, 1 H) 4.09 (s, 3 H) 4.00-4.15 (m, 2 H) 4.53 - 4.69 (m, 1 H) 6.78 (d, *J*=8.6 Hz, 1 H) 7.25 - 7.32 (m, 3 H) 7.35 (t, *J*=7.71 Hz, 1 H) 7.44 (dt, *J*=7.6, 1.5 Hz, 1 H) 7.48 - 7.54 (m, 3 H) 7.55 (t, *J*=1.8 Hz, 1 H).

Intermediario 30: 4-(3'-cloro-bifenil-4-il)-3-(2-metoxi-oxazol-5-carboxamido)-butanoato de (R)-etilo



A una solución del ácido 2-metoxi-oxazol-5-carboxílico, el intermediario 16, (98 miligramos, 0.69 milimoles) y clorhidrato de 3-amino-4-(3'-cloro-bifenil-4-il)-butanoato de (R)-etilo (210 miligramos, 0.57 milimoles) en N,N-dimetil-formamida (10 mililitros), y CH_2Cl_2 (4 mililitros), se le agregan HATU (272 miligramos, 0.72 milimoles), y

trietil-amina (0.50 mililitros, 3.58 milimoles). El producto crudo se agita a temperatura ambiente durante 2 horas. El producto crudo se apaga con agua y se diluye en EtOAc. La capa orgánica se lava con agua 3 veces, salmuera, se seca sobre $MgSO_4$, se filtra, y se concentra. El producto crudo se purifica por medio de cromatografía por evaporación instantánea utilizando desde el 30 por ciento de EtOAc/heptano hasta el 70 por ciento de EtOAc/heptano, para dar el 4-(3'-cloro-bifenil-4-il)-3-(2-metoxi-oxazol-5-carboxamido)-butanoato de (R)-etilo (122 miligramos). HPLC - tiempo de retención = 1.89 minutos (condición A); MS (m+1) = 443.2; ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 1.28 (t, *J*=7.1 Hz, 3 H), 2.52 - 2.66 (m, 2 H), 2.94 (dd, 1 H), 3.08 (dd, *J*=13.6, 6.3 Hz, 1 H), 4.12 (s, 3 H), 4.14 - 4.23 (m, 2 H), 4.60 - 4.71 (m, 1 H), 6.81 (d, *J*=8.8 Hz, 1 H), 7.25 - 7.32 (m, 3 H), 7.35 (t, *J*=7.7 Hz, 1 H), 7.42 (s, 1 H), 7.43 - 7.47 (m, 1 H), 7.48 - 7.54 (m, 2 H), 7.55 (t, *J*=1.6 Hz, 1 H).

Intermediario 31: Ácido 6-(metil-sulfonamido)-nicotínico



A una solución del 6-amino-nicotinato de metilo (1.0 gramos, 6.57 milimoles) en CH_2Cl_2 (50 mililitros) con trietil-amina (0.96 mililitros, 6.90 milimoles) enfriada en un baño de hielo, se le agrega lentamente MsCl (0.54 mililitros, 6.90 milimoles). El producto crudo se deja agitándose a temperatura ambiente durante 2 horas. El producto crudo entonces se concentra. El producto crudo se disuelve

en metanol (20 mililitros), y al producto crudo se le agrega NaOH 1 N (30 mililitros, 30 milimoles). El producto crudo se agita a temperatura ambiente durante 18 horas. El producto crudo se apaga con HCl 1N (32 mililitros, 32 milimoles). El producto crudo se concentra para remover el metanol, y también se remueve algo de agua. El producto crudo se diluye en CH_2Cl_2 y se basifica con NaOH 1 N (30 mililitros). La capa acuosa se extrae con CH_2Cl_2. La capa acuosa se acidifica con HCl concentrado para llevar el pH hasta 1 por medio de un indicador de pH de papel. El producto crudo se diluye en EtOAc, y la capa acuosa se extrae con EtOAc. La capa orgánica combinada se lava con salmuera, se seca sobre $MgSO_4$, se filtra, y se concentra, para dar el ácido 6-(metil-sulfonamido)-nicotínico (421 miligramos) como un sólido amarillo. HPLC - tiempo de retención = 0.40 minutos (condición D); MS (m+1) = 217.2.

Intermediario 32: Ácido 2-metoxi-oxazol-5-carboxílico



A una solución de 2-cloro-oxazol-5-carboxilato de etilo (510 miligramos, 2.90 milimoles) en MeCN anhidro (10 mililitros), y metanol anhidro (10 mililitros), se le agrega NaOMe (628 miligramos, 11.62 milimoles). El producto crudo se agita a reflujo durante 2 horas. Al producto crudo se le agrega metanol adicional. El producto crudo se pone a reflujo durante otras 4 horas. El producto crudo se concentra, y se vuelve a disolver en metanol (10 mililitros). Al

producto crudo se le agrega NaOH 1 N (10 mililitros). El producto crudo se agita a temperatura ambiente durante 3 horas. El producto crudo se apaga con HCl concentrado, el pH se ajusta a 7 por medio de un indicador de pH de papel. El producto crudo se concentra y se diluye en agua. La capa acuosa se acidifica con HCl concentrado, y se diluye en EtOAc. La capa orgánica se lava con agua, salmuera, se seca sobre $MgSO_4$, se filtra, y se concentra, para dar el ácido 2-metoxi-oxazol-5-carboxílico (290 miligramos). HPLC - tiempo de retención = 0.58 minutos (condición D); MS (m+1) = 144.0.

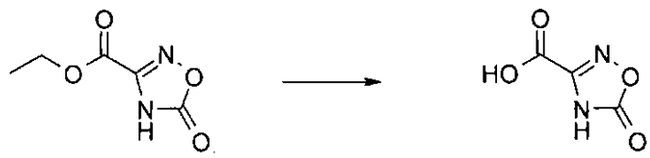
Intermediario 33: 5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-carboxilato de etilo



A una solución de 2-(hidroxi-amino)-2-imino-acetato de etilo (2 gramos, 15.14 milimoles) en dioxano (15.00 mililitros), se le agregan 1,1'-carbonil-di-imidazol (2.7 gramos, 16.65 milimoles), y DBU (2.5 mililitros, 16.65 milimoles) a temperatura ambiente. Después de agitar durante 1 hora a 80°C, la reacción se apaga con HCl 1N, y el producto crudo se diluye con EtOAc. La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida, para dar el 5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-carboxilato de etilo (2.4 gramos). HPLC - tiempo de retención = 0.72 minutos (condición D); MS 159.1 (M+1).

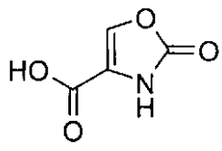
Intermediario 34: Ácido 5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-

carboxílico



A una solución del 5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-carboxilato de etilo crudo (2.4 gramos, 15.14 milimoles) en metanol (2 mililitros), se le agrega NaOH acuoso 1N (4 mililitros, 4 milimoles) a temperatura ambiente. Después de agitar durante 5 horas a temperatura ambiente, la reacción se apaga con HCl 1N (5 mililitros, 5 milimoles), y el producto crudo se concentra bajo presión reducida para remover el metanol. El producto crudo se diluye con EtOAc, la capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida, para dar el ácido 5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-carboxílico (1.9 gramos).

Intermediario 35: Ácido 2-oxo-2,3-dihidro-oxazol-4-carboxílico



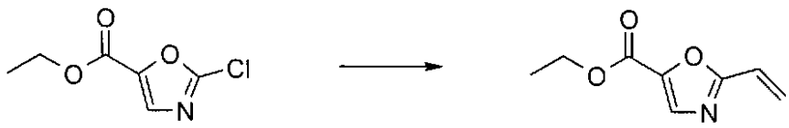
Este intermediario se prepara de acuerdo con: Okonya, J. F.; Hoffman, R. V.; Johnson, M. C.; *J. Org. Chem.* **2002**, 67, 1102-1108.

Intermediario 36: Ácido 3-hidroxi-isotiazol-5-carboxílico



A una solución de 3-hidroxi-isotiazol-5-carboxilato de metilo (300 miligramos, 1.73 milimoles) en metanol (2 mililitros), se le agrega NaOH 1N (6 mililitros, 6 milimoles). Después de agitar a temperatura ambiente durante 2 horas, el producto crudo se concentra bajo presión reducida para remover el metanol, y se diluye con EtOAc. La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida, para dar el ácido 3-hidroxi-isotiazol-5-carboxílico (250 miligramos).

Intermediario 37: 2-vinil-oxazol-5-carboxilato de etilo



A una solución del tributil-(vinil)-estanano (1.1 mililitros, 3.83 milimoles), y 2-cloro-oxazol-5-carboxilato de etilo (546 miligramos, 3.11 milimoles) en dioxano (37 mililitros), se le agrega $Pd(PPh_3)_2Cl_2$ (222 miligramos, 0.32 milimoles) a temperatura ambiente. Después de agitar a 100°C bajo nitrógeno durante 4 horas, la solución se enfría a temperatura ambiente, y entonces se apaga con H_2O. El producto crudo se diluye con EtOAc, la capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea (eluyente: heptano/EtOAc = 90:10 a 80:20), para dar el 2-vinil-oxazol-5-carboxilato de etilo (470 miligramos). HPLC - tiempo de retención = 0.39 minutos (condición B); MS (m+1) = 168.2; ^1H RMN (400 MHz,

CD_3OD) δ ppm 1.38 (t, *J*=7.1 Hz, 3 H) 4.38 (q, *J*=7.2 Hz, 2 H) 5.88 (d, *J*=11.4 Hz, 1 H) 6.39 (d, *J*=17.7 Hz, 1 H) 6.69 (dd, *J*=17.6, 11.2 Hz, 1 H) 7.83 (s, 1 H)

Intermediario 38: 2-etil-oxazol-5-carboxilato de etilo



A una solución del 2-vinil-oxazol-5-carboxilato de etilo (470 miligramos, 2.81 milimoles) en metanol (7 mililitros), se le agrega Pd/C al 10 por ciento en peso (100 miligramos, 0.094 milimoles) a temperatura ambiente. Después de agitar a temperatura ambiente bajo un globo de hidrógeno durante 1 hora, el producto crudo se filtra para remover el Pd/C. El filtrado se recolecta y se concentra, para dar el 2-etil-oxazol-5-carboxilato de etilo (470 miligramos). HPLC - tiempo de retención = 1.09 minutos (condición A); MS (m+1) = 170.3; ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.35 (t, *J*=7.6 Hz, 3 H) 1.36 (t, *J*=7.2 Hz, 3 H) 2.87 (q, *J*=7.7 Hz, 2 H) 4.35 (q, *J*=7.2 Hz, 2 H) 7.71 (s, 1 H)

Intermediario 39: Ácido 2-etil-oxazol-5-carboxílico



A una solución del oxazol-5-carboxilato de 2-etilo (470 miligramos, 2.81 milimoles) en metanol (10 mililitros), se le agrega NaOH 1N (6 mililitros, 6 milimoles). Después de agitar a temperatura

ambiente durante 18 horas, el producto crudo se concentra bajo presión reducida para remover el metanol, y se diluye con EtOAc. La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida, para dar el ácido 2-etil-oxazol-5-carboxílico (244 miligramos). ^1H RMN (400 MHz, CD_3OD) δ ppm 1.36 (t, *J*=7.7 Hz, 3 H) 2.89 (q, *J*=7.6 Hz, 2 H) 5.15 (br. s., 1 H) 7.69 (s, 1 H)

Intermediario 40: 2-vinil-tiazol-5-carboxilato de etilo



A una solución del tributil-(vinil)-estanano (0.92 mililitros, 3.14 milimoles), y 2-bromo-tiazol-5-carboxilato de etilo (0.38 mililitros, 2.54 milimoles) en dioxano (33 mililitros), se le agrega $Pd(PPh_3)_2Cl_2$ (182 miligramos, 0.26 milimoles) a temperatura ambiente. Después de agitar a 100°C bajo nitrógeno durante 4 horas, la solución se enfría a temperatura ambiente, y entonces se apaga con H_2O. El producto crudo se diluye con EtOAc, la capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida. El residuo obtenido se purifica mediante cromatografía en columna por evaporación instantánea sobre gel de sílice (eluyente: heptano/EtOAc = 90:10 a 80:20), para dar el 2-vinil-tiazol-5-carboxilato de etilo (418 miligramos). HPLC - tiempo de retención = 0.45 minutos (condición B); MS (m+1) = 184.1; ^1H RMN (400 MHz, CD_3OD) δ ppm 1.37 (t, *J*=7.2 Hz, 3 H) 4.35 (q, *J*=7.1 Hz, 2

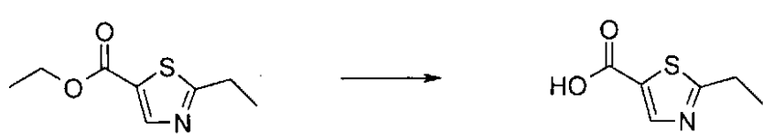
H) 5.71 (d, *J*=10.9 Hz, 1 H) 6.24 (d, *J*=17.4 Hz, 1 H) 6.93 (dd, *J*=17.4, 10.9 Hz, 1 H) 8.29 (s, 1 H)

Intermediario 41: 2-etil-tiazol-5-carboxilato de etilo



A una solución del 2-vinil-tiazol-5-carboxilato de etilo (400 miligramos, 2.18 milimoles) en metanol (7 mililitros), se le agrega Pd/C al 10 por ciento en peso (267 miligramos, 0.25 milimoles) a temperatura ambiente. Después de agitar a temperatura ambiente bajo un globo de hidrógeno durante 1 hora, el producto crudo se filtra para remover el Pd/C. El filtrado se concentra, para dar el 2-etil-tiazol-5-carboxilato de etilo (404 miligramos). HPLC - tiempo de retención = 0.60 minutos (condición B); MS (m+1) = 186.3; ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.35 (t, *J*=7.3 Hz, 2 H) 1.39 (t, *J*=7.20 Hz, 2 H) 3.07 (q, *J*=7.58 Hz, 2 H) 4.35 (q, *J*=7.16 Hz, 2 H) 8.22 (s, 1 H)

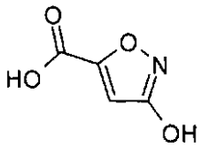
Intermediario 42: Ácido 2-etil-tiazol-5-carboxílico



A una solución del 2-etil-tiazol-5-carboxilato de etilo (400 miligramos, 2.159 milimoles) en metanol (10 mililitros), se le agrega NaOH 1N (6 mililitros, 6 milimoles). Después de agitar a temperatura ambiente durante 18 horas, el producto crudo se concentra bajo presión reducida para remover el metanol. El producto crudo se

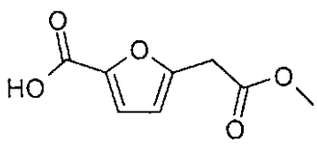
diluye con EtOAc, la capa orgánica se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra bajo presión reducida, para dar el ácido 2-etil-tiazol-5-carboxílico (282.4 miligramos). HPLC - tiempo de retención = 0.78 minutos (condición D); MS (m+3) = 160.4; ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.40 (t, *J*=7.6 Hz, 3 H) 3.07 (q, *J*=7.6 Hz, 2 H) 5.08 (br. s., 1 H) 8.20 (s, 1 H).

Intermediario 43: Ácido 3-hidroxi-isoxazol-5-carboxílico



A una solución del metil-éster del ácido 3-hidroxi-isoxazol-5-carboxílico (286 miligramos, 2.0 milimoles) en metanol (7 mililitros), se le agrega NaOH 1N (4.0 mililitros, 4.0 milimoles), y la mezcla se agita a temperatura ambiente durante 18 horas. El solvente se remueve bajo presión reducida, y al residuo se le agregan 4.0 mililitros de HCl 1N. La solución resultante se liofiliza para dar el producto, el cual se utiliza como está en las siguientes reacciones.

Intermediario 44: Ácido 5-metoxi-carbonil-metil-furan-2-carboxílico

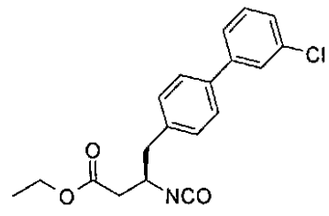


A una solución del metil-éster del ácido 5-metoxi-carbonil-metil-furan-2-carboxílico (250 miligramos, 1.26 milimoles) en metanol (5 mililitros), se le agrega NaOH 1N (2.78 mililitros, 2.78 milimoles),

y la mezcla se agita a temperatura ambiente durante 18 horas. El solvente se remueve bajo presión reducida, y se agregan al residuo 2.78 mililitros de HCl 1N. La solución resultante se liofiliza para dar el ácido 5-carboxi-metil-furan-2-carboxílico.

En seguida, a una solución del diácido anterior (220 miligramos, 1.29 milimoles) en metanol (8 mililitros), se le agrega resina Amberlyst-15 (50 miligramos), y la mezcla se agita a temperatura ambiente durante 18 horas. La resina se filtra y el solvente se remueve bajo presión reducida, para dar el producto, el cual se utiliza como está en las siguientes reacciones. ^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 3.75 (s, 3H), 3.82 (s, 2H), 6.45 (d, J=3.54 Hz, 1H), 7.29 (d, J=3.54 Hz, 1H), 10.17 (s, amplia, 1H).

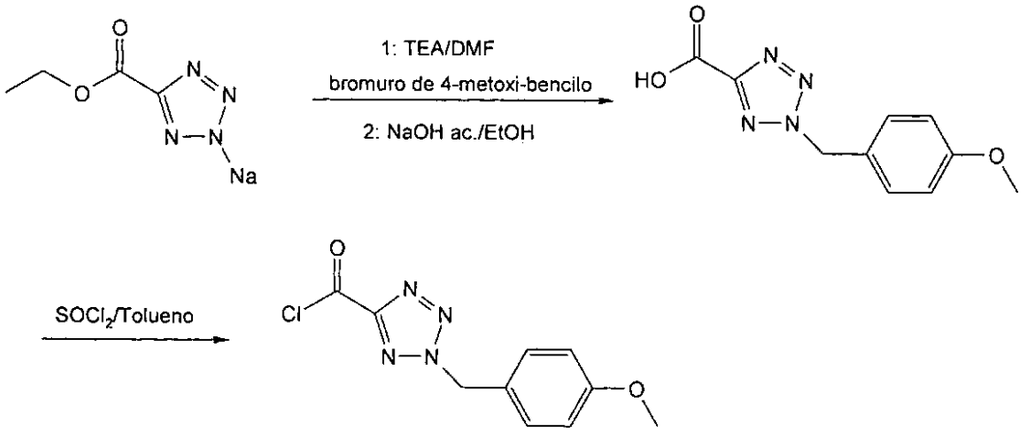
Intermediario 45: Etil-éster del ácido (R)-4-(3'-cloro-bifenil-4-il)-3-isocianato-butírico



A una mezcla vigorosamente agitada de acuoso bicarbonato de sodio al 8 por ciento (3 mililitros), y cloruro de metileno (3 mililitros) a 0°C, se le agrega trifosgeno (28.1 miligramos, 0.095 milimoles), y la mezcla se agita a 0°C durante 5 minutos; entonces se agrega el intermediario 17-1 (100 miligramos, 0.284 milimoles), y la agitación se continúa durante 15 minutos adicionales. La capa orgánica se separa y se seca sobre sulfato de sodio. El solvente se remueve bajo

presión reducida, para dar el compuesto del título. Éste se utiliza como está en las siguientes reacciones.

Intermediario 46: Cloruro de 2-(4-metoxi-bencil)-2H-tetrazol-5-carbonilo

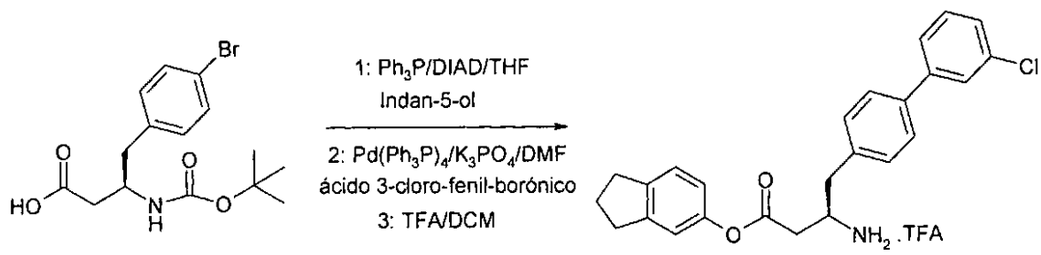


A una solución de la sal de sodio del etil-éster del ácido 1H-tetrazol-5-carboxílico (500 miligramos, 3.05 milimoles) en N,N-dimetil-formamida (5 mililitros) a temperatura ambiente, se le agregan 4-metoxi-cloruro de bencilo (747 microlitros, 5.48 milimoles), y trietil-amina (1500 microlitros, 10.76 milimoles). La mezcla de reacción se agita a temperatura ambiente durante la noche. A la reacción se le agrega agua, y se extrae con EtOAc. La capa orgánica combinada se lava con salmuera, y se seca sobre sulfato de sodio anhidro, se filtra, y se concentra bajo presión reducida. El residuo se purifica mediante cromatografía en columna (del 10 por ciento al 30 por ciento de EtOAc/Heptano). A una solución del residuo purificado

en EtOH (2 mililitros) a temperatura ambiente, se le agrega NaOH (2 mililitros, 2.000 milimoles), y la mezcla se agita a temperatura ambiente. Después de agitar durante 1 hora, la mezcla se concentra bajo presión reducida para remover el EtOH, y se extrae con EtOAC después de acidificarse a un pH <5. La capa orgánica combinada se lava con salmuera, y se seca sobre sulfato de sodio anhidro, se filtra, y se concentra bajo presión reducida, para dar el ácido 2-(4-metoxi-bencil)-2H-tetrazol-5-carboxílico.

En seguida, a una mezcla del ácido 2-(4-metoxi-bencil)-2H-tetrazol-5-carboxílico en tolueno (15 mililitros) a temperatura ambiente, se le agrega $SOCl_2$ (1 mililitro, 13.70 milimoles), y la mezcla se calienta a 80°C durante 3 horas. La mezcla de reacción se concentra bajo presión reducida, para dar el producto crudo, el cual se utiliza sin mayor purificación.

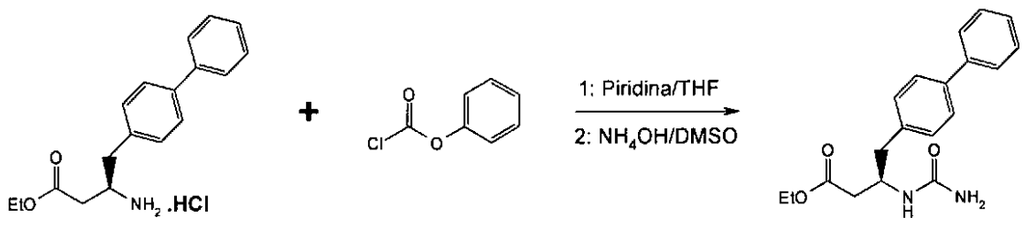
Intermediario 47: Indan-5-il-éster del ácido (R)-3-amino-4-(3'-cloro-bifenil-4-il)-butírico



A una suspensión del ácido boc-(R)-3-amino-4-(4-bromo-fenil)-butanoico (500 miligramos, 1.396 milimoles) en tetrahidrofurano (12 mililitros) a temperatura ambiente, se le agregan 5-indanol (187 miligramos, 1.396 milimoles), y Ph_3P (403 miligramos, 1.535

milimoles). A la mezcla en un baño de hielo, se le agrega DIAD (0.326 mililitros, 1.675 milimoles), y la mezcla se agita a partir del baño de hielo a temperatura ambiente durante la noche. La reacción se concentra bajo presión reducida, y se purifica mediante cromatografía en columna (del 5 por ciento al 20 por ciento de EtOAc/Heptano), para dar 450 miligramos de un sólido. A una solución del sólido obtenido (200 miligramos, 0.422 milimoles) en N,N-dimetil-formamida (5 mililitros) a temperatura ambiente, se le agregan ácido 3-cloro-fenil-borónico (79 miligramos, 0.506 milimoles), trifosfato de potasio (134 miligramos, 0.632 milimoles), y $Pd(PPh_3)_4$ (48.7 miligramos, 0.042 milimoles). La reacción se agita a 100°C durante la noche. La reacción se apaga con salmuera, y se extrae con EtOAc. La capa orgánica combinada se lava con salmuera, y se seca sobre sulfato de sodio anhidro, se filtra, y se concentra bajo presión reducida. El residuo se purifica mediante cromatografía en columna (del 5 por ciento al 30 por ciento de EtOAc/Heptano). Al residuo obtenido (143 miligramos, 0.283 milimoles) en dicloro-metano (1 mililitro) a temperatura ambiente, se le agrega ácido trifluoro-acético (1 mililitro, 12.98 milimoles), y la mezcla se agita a temperatura ambiente durante 2 horas. La mezcla se concentra, para dar la sal cruda, la cual se utiliza directamente sin mayor purificación. HPLC - tiempo de retención = 1.27 minutos (condición B); MS (m+1) = 406.

Intermediario 48: Etil-éster del ácido (R)-4-bifenil-4-il-3-ureido-butírico

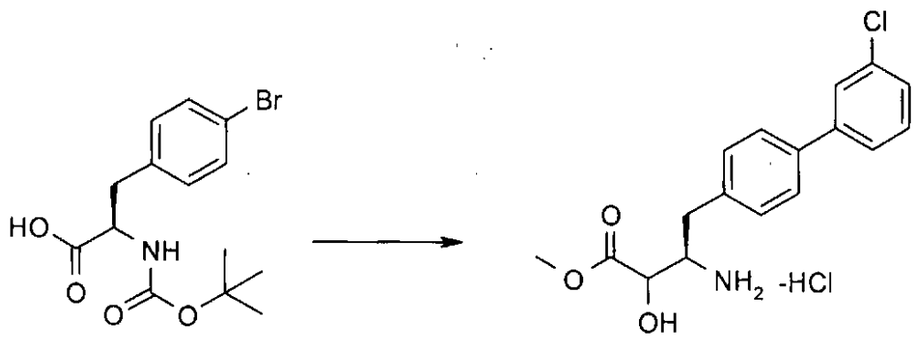


A una suspensión del etil-éster del ácido (R)-3-amino-4-bifenil-4-il-butírico (200 miligramos, 0.625 milimoles) en tetrahidrofurano (10 mililitros) a 0°C, se le agregan cloroformato de fenilo (0.087 mililitros, 0.688 milimoles), y piridina (0.126 mililitros, 1.563 milimoles). La mezcla se agita a 0°C durante 5 minutos, y entonces se calienta hasta la temperatura ambiente. La LCMS monitorea la reacción hasta completarse. La reacción se extrae con EtOAc. La capa orgánica combinada se lava con HCl 1N, H_2O, $NaHCO_3$ acuoso saturado y salmuera, y se seca sobre sulfato de sodio anhidro, se filtra, y se concentra, para dar el residuo crudo.

En seguida, a una solución del residuo obtenido (0.252 gramos, 0.625 milimoles) en sulfóxido de dimetilo (1.5 mililitros) a temperatura ambiente, se le agrega hidróxido de amonio (0.027 mililitros, 0.688 milimoles). La reacción se agita a temperatura ambiente durante 30 minutos. La LCMS muestra un pequeño producto deseado con un material de partida grande, de manera que se agrega más hidróxido de amonio, y la reacción se agita a temperatura ambiente durante la noche hasta que se completa la reacción. La reacción se extrae con EtOAc. La capa orgánica combinada se lava con H_2O, HCl 1N, H_2O, NaOH 1 N y salmuera, y

se seca sobre sulfato de sodio anhidro, se filtra, y se concentra bajo presión reducida. El residuo se purifica mediante cromatografía en columna (del 2 por ciento al 6 por ciento de EtOH/DCM), para dar el etil-éster del ácido (R)-4-bifenil-4-il-3-ureido-butírico (169 miligramos). HPLC - tiempo de retención = 1.04 minutos (condición B); MS (m+1) = 327.

Intermediario 49: Clorhidrato de metil-éster del ácido (R)-3-amino-4-(3'-cloro-bifenil-4-il)-2-hidroxi-butírico



El ácido (R)-3-(4-bromo-fenil)-2-terbutoxi-carbonil-amino-propiónico (4.0 gramos, 11.6 milimoles), el ácido 3-cloro-fenil-borónico (2.36 gramos, 15.11 milimoles), $Pd(PPh_3)_4$ (0.067 gramos, 0.058 milimoles), y una solución acuosa de Na_2CO_3 2M (8.0 mililitros), se ponen a reflujo en 1,2-dimetoxi-etano (70 mililitros) durante 2.5 horas bajo una atmósfera de N_2. Después de enfriar a temperatura ambiente, la mezcla de reacción se diluye con EtOAc, y se lava con HCl 1M y salmuera. La capa orgánica se seca sobre Na_2SO_4 y se concentra. El residuo se purifica mediante cromatografía en columna por evaporación instantánea (gel de sílice, DCM/MeOH al 10 por ciento en dicloro-metano = 100:0 a 0:100), para

dar el ácido (R)-2-terbutoxi-carbonil-amino-3-(3'-cloro-bifenil-4-il)-propiónico (que contiene impurezas). HPLC - tiempo de retención = 1.56 minutos (condición A): MS (m+1) = 376.

Éste se disuelve en 1, 2-dimetoxi-etano (40 mililitros) y Et_3N (1.46 mililitros, 10.5 milimoles), y se agrega cloro-formato de etilo (1.00 mililitros, 10.5 milimoles). Después de agitarse a temperatura ambiente durante 0.5 horas, el precipitado resultante se remueve mediante filtración. Al filtrado se le agrega lentamente $NaBH_4$ (0.44 gramos, 11.6 milimoles) en H_2O (5 mililitros). Después de agitarse durante 2 horas, la mezcla de reacción se diluye con EtOAc, y se lava con H_2O y salmuera. La capa orgánica se seca sobre Na_2SO_4, se concentra, y se purifica mediante cromatografía en columna por evaporación instantánea (gel de sílice, eluyente; heptano/EtOAc = 100:0 a 0:100), para dar el terbutil-éster del ácido [(R)-2-(3'-cloro-bifenil-4-il)-1-hidroxi-metil-etil]-carbámico (2.8 gramos). HPLC - tiempo de retención = 1.26 minutos (condición A): MS (m+1-Boc) = 262. 1H-RMN (400 MHz, DMSO-d6) δ ppm 1.43 (s, 9 H), 2.90 (d, 2 H, *J* = 7.33 Hz), 3.60 (dd, 1 H, *J* = 5.05, 10.86 Hz), 3.72 (dd, 1 H, *J* = 3.79, 11.12 Hz), 3.91 (bs, 1 H), 4.75 (bs, 1 H), 7.29-7.34 (m, 3 H), 7.37 (t, 1 H, *J* = 7.83 Hz), 7.44-7.48 (m, 1 H), 7.51 (d, 2 H, *J* = 8.08 Hz), 7.57 (t, 1 H, *J* = 1.77 Hz).

En seguida, a una solución del terbutil-éster del ácido [(R)-2-(3'-cloro-bifenil-4-il)-1-hidroxi-metil-etil]-carbámico (2.0 gramos, 5.53 milimoles) en dicloro-metano (30 mililitros), se le agrega peryodinano Dess-Martin (2.81 gramos, 6.63 milimoles). Después de agitarse a

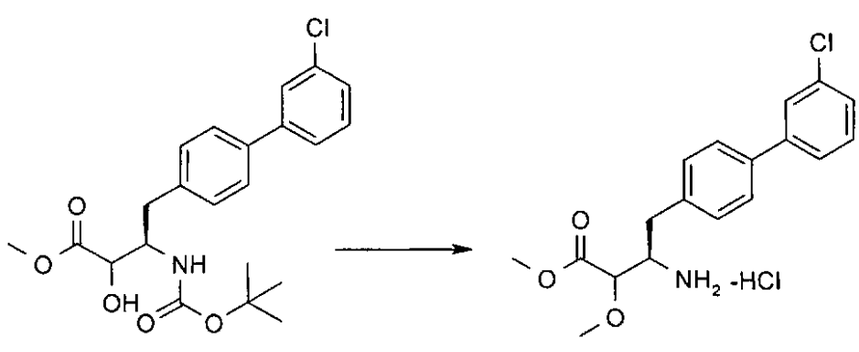
temperatura ambiente durante 2 horas, la mezcla de reacción se diluye con EtOAc, y se lava con una solución acuosa saturada de $NaHCO_3$ y salmuera. La capa orgánica se seca sobre Na_2SO_4 y se concentra. El residuo se purifica mediante cromatografía en columna por evaporación instantánea (gel de sílice, eluyente; heptano/EtOAc = 100:0 a 0:100), para dar el terbutil-éster del ácido [(R)-2-(3'-cloro-bifenil-4-il)-1-formil-etil]-carbámico (1.05 gramos). HPLC - tiempo de retención = 1.27 minutos (condición A): MS (m+1) = 360.

Éste se disuelve en metanol (20 mililitros) y AcOH (0.199 mililitros, 3.47 milimoles). A esta solución se le agrega lentamente KCN (0.226 gramos, 3.47 milimoles) en H_2O (4 mililitros). Después de agitarse a temperatura ambiente durante la noche, la mezcla de reacción se diluye con EtOAc, y se lava con una solución acuosa saturada de $NaHCO_3$, H_2O y salmuera. La capa orgánica se seca sobre Na_2SO_4 y se concentra. Ésta se trata con HCl 4M en dioxano (20 mililitros) y metanol (10 mililitros) a temperatura ambiente. Después de agitarse durante la noche, la mezcla de reacción se concentra. El residuo se disuelve en metanol, y se trata con $SOCl_2$ (0.211 mililitros, 2.89 milimoles). Después de agitarse a 50°C durante 5 horas, la mezcla de reacción se concentra a sequedad. El residuo se disuelve en tetrahidrofurano (10 mililitros), y se trata con una solución acuosa saturada de $NaHCO_3$ (5 mililitros) y Boc_2O (0.631 gramos, 2.89 milimoles). Después de agitarse a temperatura ambiente durante 2 horas, la mezcla de reacción se diluye con EtOAc, y se lava con salmuera. La capa orgánica se seca sobre

$MgSO_4$ y se concentra. El residuo se purifica mediante cromatografía en columna por evaporación instantánea (gel de sílice, eluyente; heptano/EtOAc = 100:0 a 0:100), para dar el metil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-2-hidroxi-butírico (0.61 gramos). HPLC - tiempo de retención = 1.01, 1.06 minutos (condición B): MS (m+1-Boc) = 320. 1H-RMN (400 MHz, $CDCl_3$) δ ppm 1.40 (s, 9 H), 2.77-3.05 (m, 2 H), 3.63 (s, 0.7 H), 3.77 (s, 2.3 H), 4.11 (s, 0.8 H), 4.25-4.40 (m, 1.2 H), 4.78-4.95 (m, 1 H), 7.27-7.40 (m, 4 H), 7.42-7.58 (m, 4 H).

El metil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-2-hidroxi-butírico (113 miligramos, 0.269 milimoles), se trata con HCl 4M en dioxano (2 mililitros). Después de agitarse a temperatura ambiente durante 1 hora, la mezcla de reacción se concentra. El residuo se utiliza para el siguiente paso sin mayor purificación. HPLC - tiempo de retención = 1.22, 1.29 minutos (condición A): MS (m+1) = 320.

Intermediario 50: clorhidrato de metil-éster del ácido (R)-3-amino-4-(3'-cloro-bifenil-4-il)-2-metoxi-butírico

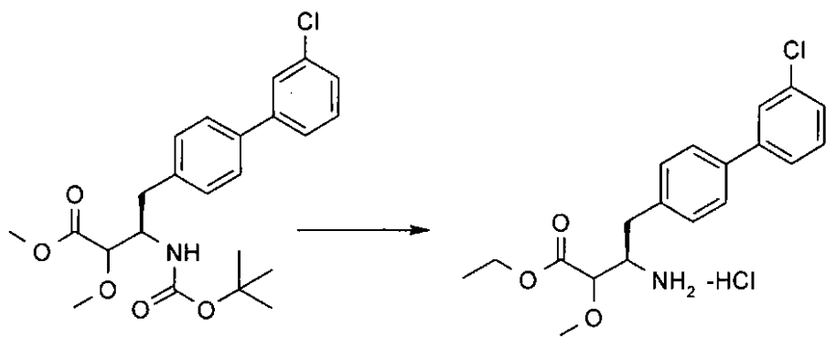


A una solución del metil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-2-hidroxi-butírico (610 miligramos, 1.45 milimoles) en CH_3CN (20 mililitros), se le agregan yodo-metano (0.545 mililitros, 8.72 milimoles), y óxido de plata (1.35 gramos, 5.81 milimoles). Después de agitarse a temperatura ambiente durante 16 horas, se agregan yodo-metano (0.545 mililitros, 8.72 milimoles), y óxido de plata adicionales (1.35 gramos, 5.81 milimoles), y se agitan durante 3 días. La mezcla de reacción se filtra a través de un cojín de Celite, y el filtrado se lava con salmuera. La capa orgánica se seca sobre $MgSO_4$ y se concentra. El residuo se purifica mediante cromatografía en columna por evaporación instantánea (gel de sílice, eluyente; heptano/EtOAc = 100:0 a 0:100), para dar el metil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-2-metoxi-butírico (500 miligramos). HPLC - tiempo de retención = 1.20, 1.25 minutos (condición B): MS (m+1-Boc) = 334. 1H-RMN (400 MHz, $CDCl_3$) δ ppm 1.37, 1.41 (s, 9 H), 2.72-3.03 (m, 2 H), 3.43, 3.71 (s, 3H), 3.63-3.82 (m, 1 H), 4.27-4.41 (m, 1 H), 4.68-5.04 (m, 1 H), 7.28-7.40 (m, 4 H), 7.41-7.61 (m, 4 H).

El metil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-2-metoxi-butírico (200 miligramos, 0.461 milimoles), se trata con HCl 4M en dioxano (3 mililitros). Después de agitarse a temperatura ambiente durante 1 hora, la mezcla de reacción se concentra. El residuo se utiliza para el siguiente paso sin mayor

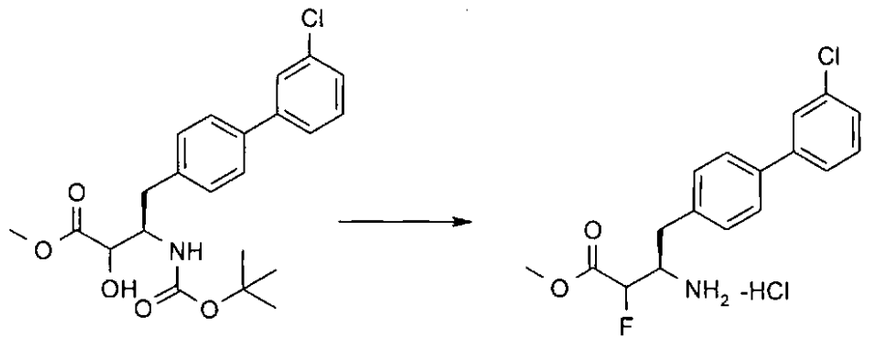
purificación. HPLC - tiempo de retención = 1.26, 1.33 minutos (condición A): MS (m+1) = 334.

Intermediario 51: Clorhidrato de etil-éster del ácido (R)-3-amino-4-(3'-cloro-bifenil-4-il)-2-metoxi-butírico



A una solución del metil-éster del ácido (R)-3-amino-4-(3'-cloro-bifenil-4-il)-2-metoxi-butírico (500 miligramos, 1.15 milimoles) en metanol (5 mililitros), se le agrega una solución acuosa de NaOH 2M (5 mililitros). Después de agitarse a temperatura ambiente durante 2 horas, la mezcla de reacción se acidifica con HCl 2M y se extrae con EtOAc. La capa orgánica se seca sobre Na_2SO_4 y se concentra. El residuo se disuelve en EtOH (5 mililitros), y se trata con $SOCl_2$ (0.252 mililitros, 3.26 milimoles). Después de agitarse a 55°C, la mezcla de reacción se concentra. El residuo se utiliza para el siguiente paso sin mayor purificación. HPLC - tiempo de retención = 1.49 minutos (condición A): MS (m+1) = 348.2

Intermediario 52: Clorhidrato de metil-éster del ácido (R)-3-amino-4-(3'-cloro-bifenil-4-il)-2-fluoro-butírico

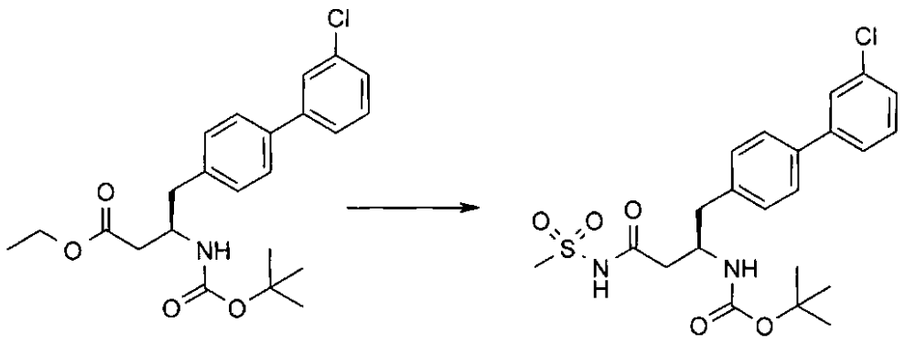


A una solución del metil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-2-hidroxi-butírico (220 miligramos, 0.524 milimoles), se le agrega DAST (0.083 mililitros, 0.629 milimoles) a 0°C. La mezcla de reacción se calienta gradualmente a temperatura ambiente, y se agita durante 1 hora. Se agrega DAST adicional (0.083 mililitros, 0.629 milimoles), y se agita a temperatura ambiente durante 2 horas. La mezcla de reacción se diluye con EtOAc, y se lava con una solución acuosa saturada de $NaHCO_3$ y salmuera. La capa orgánica se seca sobre Na_2SO_4 y se concentra. El residuo se purifica mediante cromatografía en columna por evaporación instantánea (gel de sílice, eluyente; heptano/EtOAc = 100:0 a 0:100), para dar el metil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-2-fluoro-butírico (63 miligramos). HPLC - tiempo de retención = 1.36 minutos (condición B): MS (m+1-Boc) = 322.1H-RMN (400 MHz, $CDCl_3$) δ ppm 1.39 (s, 9 H), 2.84-2.95 (m, 2 H), 3.06 (bs, 0.5 H), 3.69 (s, 3 H), 4.43-4.61 (m, 1 H), 4.72-4.80 (m, 0.5 H), 5.00 (s, 0.5 H), 5.12 (s, 0.5 H), 7.28-7.34 (m, 3 H), 7.37 (t, 1 H, *J* = 7.58 Hz), 7.42-7.47 (m, 1 H), 7.48-7.53 (m, 1 H), 7.55 (t, 1 H, *J* = 2.02 Hz). 19F-RMN (377 MHz, $CDCl_3$) δ ppm -

204.18.

El metil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-2-fluoro-butírico (60 miligramos, 0.142 milimoles), se trata con HCl 4M en dioxano (1.5 mililitros). Después de agitarse a temperatura ambiente durante 1 hora, la mezcla de reacción se concentra. El residuo se utiliza para el siguiente paso sin mayor purificación. HPLC - tiempo de retención = 0.88 minutos (condición B): MS (m+1) = 322.

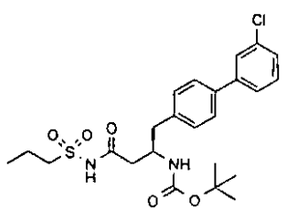
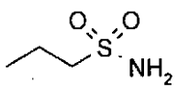
Intermediario 53-1: Terbutil-éster del ácido [(R)-1-(3'-cloro-bifenil-4-il-metil)-3-metan-sulfonil-amino-3-oxo-propil]-carbámico

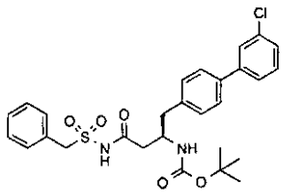
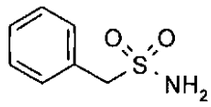
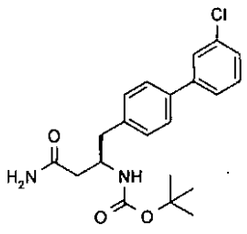


El etil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-butírico (250 miligramos, 0.598 milimoles) se trata con una solución acuosa de NaOH 2M (1 mililitro) en tetrahidrofurano (1 mililitro) y EtOH (2 mililitros). Después de agitarse durante 1 hora, la mezcla de reacción se acidifica con HCl 1M, y se extrae con EtOAc. La capa orgánica se lava con salmuera, se seca sobre Na_2SO_4 y se concentra al vacío. A una solución de este residuo en N,N-dimetil-formamida (2 mililitros) se le agregan metil-sulfonamida (85 miligramos, 0.897 milimoles), EDC (172 miligramos, 0.897

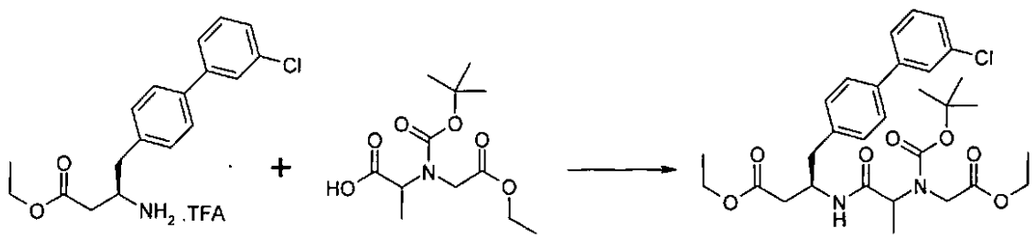
milimoles), HOAt (98 miligramos, 0.718 milimoles), y Et_3N (0.125 mililitros, 0.897 milimoles). Después de agitarse a temperatura ambiente durante la noche, la mezcla de reacción se diluye con EtOAc, se lava con HCl 1M y salmuera. La capa orgánica se seca sobre Na_2SO_4 y se concentra. El residuo se purifica mediante cromatografía en columna por evaporación instantánea (gel de sílice, eluyente: DCM/MeOH al 10 por ciento en dicloro-metano = 100:0 a 0:100), para dar el terbutil-éster del ácido [(R)-1-(3'-cloro-bifenil-4-il-metil)-3-metan-sulfonil-amino-3-oxo-propil]-carbámico (244 miligramos). HPLC tiempo de retención = 1.30 minutos (condición B); MS (m+1) = 467; ^{1}H RMN (400 Mz, DMSO-d6) δ ppm 1.30 (s, 9 H), 2.41-2.48 (m, 2 H), 2.70-2.78 (m, 2 H), 3.18 (s, 3 H), 3.99-4.11 (m, 1 H), 7.28 (d, 2 H, *J* = 8.34 Hz), 7.38-7.44 (m, 1 H), 7.48 (t, 1 H, *J* =7.83 Hz), 7.59-7.66 (m, 3 H), 7.69 (s, 1 H).

Se preparan los siguientes compuestos empleando un procedimiento similar al que se describe en el Ejemplo 53-1:

Ejemplo	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
Ejemplo 53-2			1.22 minutos. (condición B)	496

Ejemplo	Producto	Reactivo	HPLC-RT (condición)	MS (M+1)
Ejemplo 53-3			1.33 minutos. (condición B)	544
Ejemplo 53-4		NH_4Cl	1.17 minutos. (condición B)	389

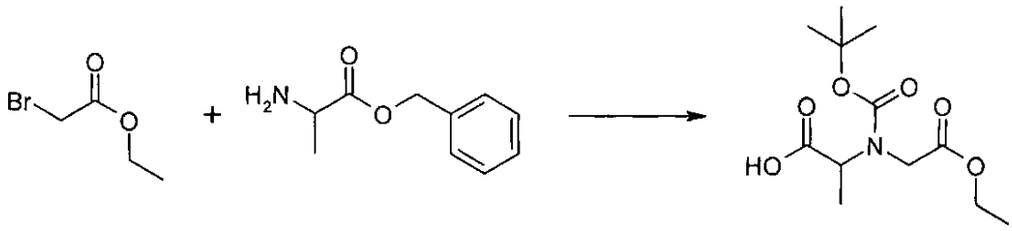
Intermediario 54-1: Etil-éster del ácido (R)-3-[2-(terbutoxi-carbonil-etoxi-carbonil-metil-amino)-propionil-amino]-4-(3'-cloro-bifenil-4-il)-butírico



A una suspensión de la sal de ácido trifluoro-acético del ácido 2-(terbutoxi-carbonil-etoxi-carbonil-metil-amino)-propiónico (197 miligramos, 0.714 milimoles) en tetrahidrofurano (10 mililitros) a temperatura ambiente, se le agregan EDCI (219 miligramos, 1.142 milimoles), y HOBT (164 miligramos, 1.071 milimoles). La mezcla se

agita a temperatura ambiente durante 10 minutos, y entonces se le agrega una solución de etil-éster del ácido (R)-3-amino-4-(3'-cloro-bifenil-4-il)-butírico (202 miligramos, 0.571 milimoles) en tetrahidrofurano y trietil-amina (0.199 mililitros, 1.428 milimoles). La mezcla se agita a temperatura ambiente. La HPLC en fase inversa [del 30 al 90 por ciento de ACN-H_2O (ácido trifluoro-acético al 0.1 por ciento) durante 10 minutos mediante columna de fenilo X-Bridge] da el compuesto del título (290 miligramos, 71 por ciento de rendimiento). LCMS (condición B): 575 (M+1); tiempo de retención = 1.52 minutos.

Intermediario 54-2: Ácido 2-(terbutoxi-carbonil-etoxi-carbonil-metil-amino)-propiónico



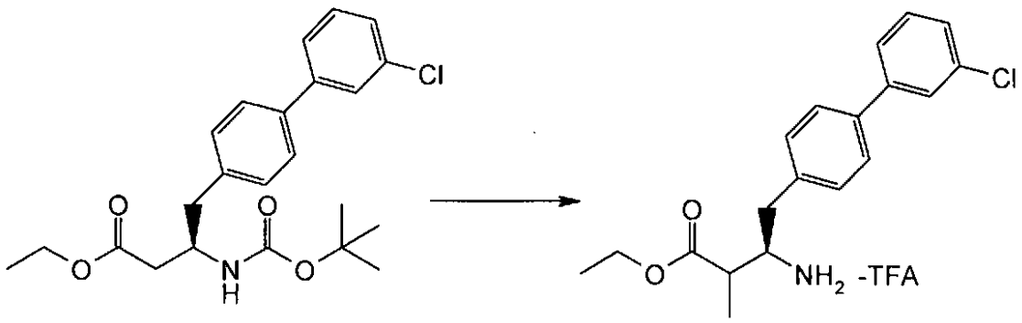
A una solución de H-DL-Ala-OBzl.p-tosilato (2.88 gramos, 8.20 milimoles) en tetrahidrofurano (80 mililitros) a temperatura ambiente se le agrega trietil-amina (3.43 mililitros, 24.60 milimoles), seguida por bromo-acetato de etilo (1.096 mililitros, 9.84 milimoles). La reacción se agita a temperatura ambiente durante la noche. Hay algo de un sólido blanco en la reacción. La mezcla de reacción se filtra, y el sólido blanco se concentra para la purificación. La cromatografía por evaporación instantánea (gel de sílice, del 2 al 4 por ciento de

EtOH/DCM) da el compuesto del título como un aceite (1.7 gramos, 78 por ciento de rendimiento). LCMS (condición B): 266 (M+1); tiempo de retención = 0.70 minutos.

En seguida, a una solución del bencil-éster del ácido 2-(etoxi-carbonil-metil-amino)-propiónico (1.7 gramos, 6.41 milimoles) en dicloro-metano (80 mililitros) a 0°C, se le agrega anhídrido de Boc (2.232 mililitros, 9.61 milimoles), seguido por trietil-amina (2.68 mililitros, 19.22 milimoles). La mezcla de reacción se calienta lentamente hasta la temperatura ambiente, y se agita durante la noche. La reacción se apaga con salmuera, y se extrae con dicloro-metano. La capa orgánica combinada se lava con salmuera, y se seca sobre sulfato de sodio anhidro, se filtra, y se concentra, para dar el producto crudo. La cromatografía por evaporación instantánea (gel de sílice, del 5 al 10 por ciento de acetona/heptano) da el compuesto del título como un aceite (1.66 gramos, 71 por ciento de rendimiento). LCMS (condición B): 366 (M+1); tiempo de retención = 1.13 minutos.

En seguida, una solución del bencil-éster del ácido 2-(terbutoxi-carbonil-etoxi-carbonil-metil-amino)-propiónico en EtOAc se hidrogena bajo un globo de H_2 mediante el catalizador de Pd/C al 10 por ciento húmedo durante 1 hora. La reacción se filtra, y el catalizador se concentra, para dar el producto crudo para la siguiente reacción.

Intermediario 55: Trifluoro-acetato de etil-éster del ácido (R)-3-amino-4-(3'-cloro-bifenil-4-il)-2-metil-butírico



A una solución del etil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-butírico (300 miligramos, 0.718 milimoles) en tetrahidrofurano (10 mililitros) a -78°C, se le agrega LiHMDS/THF (1M) (1.579 mililitros, 1.579 milimoles). La mezcla de reacción se agita a -78°C durante 50 minutos, y entonces a esta mezcla se le agrega yodo-metilo (0.054 mililitros, 0.861 milimoles), y la reacción se calienta lentamente hasta la temperatura ambiente, y se agita durante la noche. La reacción se apaga con NH_4Cl saturado, y se extrae con EtOAc. La capa orgánica combinada se lava con salmuera, y se seca sobre sulfato de sodio anhidro, se filtra, y se concentra, para dar el producto crudo. La HPLC en fase inversa [del 20 al 90 por ciento de ACN-H_2O (ácido trifluoro-acético al 0.1 por ciento) durante 10 minutos mediante Sunfire C18] da el etil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-2-metil-butírico. LCMS (condición B): 432 (M+1); tiempo de retención = 1.55 minutos. A una solución del etil-éster del ácido (R)-3-terbutoxi-carbonil-amino-4-(3'-cloro-bifenil-4-il)-2-metil-butírico (240 miligramos, 0.556 milimoles) en dicloro-metano (2 mililitros) a temperatura ambiente, se le agrega ácido trifluoro-acético (1.070

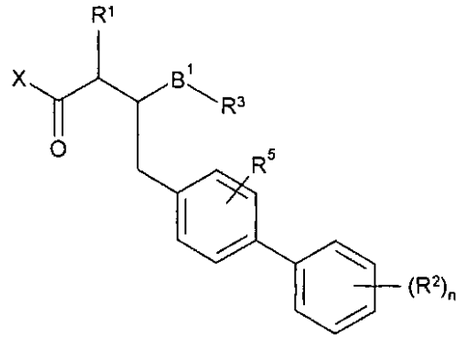
mililitros, 13.89 milimoles), y la mezcla se agita a temperatura ambiente durante 1 hora. La reacción queda hecha, de modo que la mezcla se concentra, para dar el trifluoro-acetato de etil-éster del ácido (R)-3-amino-4-(3'-cloro-bifenil-4-il)-2-metil-butírico. LCMS (condición B): 332 (M+1); tiempo de retención = 1.00 minutos.

Se puede ver que los compuestos de la invención son útiles como inhibidores de la actividad de la endopeptidasa neutra (EC 3.4.24.11) y, por consiguiente, son útiles en el tratamiento de enfermedades y condiciones asociadas con la actividad de la endopeptidasa neutra (EC 3.4.24.11), tales como las enfermedades que se dan a conocer en la presente.

Se entenderá que la invención se ha descrito a manera de ejemplo solamente, y que se pueden hacer modificaciones mientras que permanezcan dentro del alcance y espíritu de la invención.

REIVINDICACIONES

1. Un compuesto de la fórmula I':



Fórmula I'

o una sal farmacéuticamente aceptable del mismo, en donde:

R^1 es H, alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, -SH, -S-alquilo de 1 a 7 átomos de carbono o NR^aR^b;

R^2 por cada presentación, es independientemente alquilo de 1 a 7 átomos de carbono, halógeno, NO_2, CN, alcanoílo de 1 a 7 átomos de carbono-amino, cicloalquilo de 3 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, $-NR^aR^b$, arilo de 6 a 10 átomos de carbono, heteroarilo o heterociclilo; en donde R^a y R^b por cada presentación, son independientemente H o alquilo de 1 a 7 átomos de carbono;

R^3 es A^1-$C(O)X^1$ o A^2-R^4;

R^4 es arilo de 6 a 10 átomos de carbono, o un heteroarilo, el cual puede ser monocíclico o bicíclico, y el cual puede

estar opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en hidroxilo, hidroxi-alquilo de 1 a 7 átomos de carbono, nitro, $-NR^aR^b$, -C(O)-alquilo de 1 a 7 átomos de carbono, C(O)-O-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, alquenilo de 2 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, heteroarilo, $-NHSO_2$-alquilo de 1 a 7 átomos de carbono y bencilo; o R^4 es un heterociclilo, el cual puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en oxo, hidroxilo, hidroxi-alquilo de 1 a 7 átomos de carbono, amino, C(O)-O-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, heteroarilo, $-NHSO_2$-alquilo de 1 a 7 átomos de carbono y bencilo;

R^5 es H, halógeno, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, o halo-alquilo de 1 a 7 átomos de carbono; y

X y X^1 son independientemente OH, -O-alquilo de 1 a 7 átomos de carbono, $-NR^aR^b$, $-NHS(O)_2$-alquilo de 1 a 7 átomos de carbono, $-NHS(O)_2$-bencilo u -O-arilo de 6 a 10 átomos de carbono; en donde el alquilo está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en arilo de 6 a 10 átomos de carbono, heteroarilo,

heterociclilo, $C(O)NH_2$, C(O)NH-alquilo de 1 a 6 átomos de carbono, y C(O)N(alquilo de 1 a 6 átomos de carbono)$_2$;

B^1 es –C(O)NH- o –NHC(O)-;

A^1 es un enlace o un alquileno de 1 a 7 átomos de carbono lineal o ramificado, que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno, cicloalquilo de 3 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, y O-acetato; en donde dos grupos alquilo geminales pueden combinarse opcionalmente para formar un cicloalquilo de 3 a 7 átomos de carbono; o

A^1 es un alquenileno de 1 a 7 átomos de carbono lineal o ramificado; o

A^1 es un alquileno lineal de 1 a 4 átomos de carbono, en donde uno o más átomos de carbono son reemplazados con un heteroátomo seleccionado a partir de O, NR^c; y A^1 está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno y alquilo de 1 a 7 átomos de carbono; en donde R^c por cada presentación, es independientemente H, alquilo de 1 a 7 átomos de carbono, -C(O)-O-alquilo de 1 a 7 átomos de carbono, o $-CH_2C(O)OH$; o

A^1 es un fenilo o un heteroarilo; cada uno de los cuales está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en

alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, $-NR^aR^b$, $-OCH_2CO_2H$, y $-OCH_2C(O)NH_2$; o

A^1 es un cicloalquilo de 3 a 7 átomos de carbono;

A^1 es -alquileno de 1 a 4 átomos de carbono-arilo de 6 a 10 átomos de carbono-, -alquileno de 1 a 4 átomos de carbono-heteroaril-, o -alquileno de 1 a 4 átomos de carbono-heterociclil-, en donde A^1 puede estar en cualquier dirección; y

A^2 es un enlace o un alquileno de 1 a 7 átomos de carbono lineal o ramificado, que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, O-acetato y cicloalquilo de 3 a 7 átomos de carbono;

n es 0, 1, 2, 3, 4 ó 5;

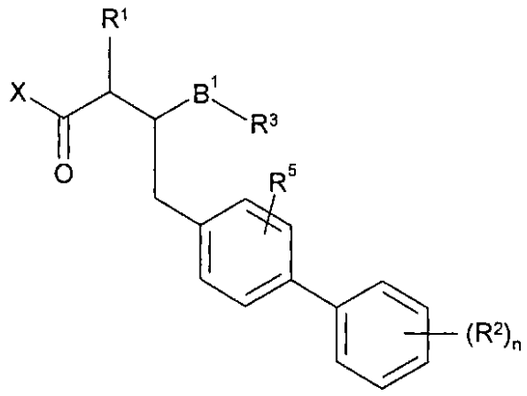
en donde cada heteroarilo es un anillo aromático monocíclico o bicíclico que comprende de 5 a 10 átomos del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, y

cada heterociclilo es una fracción monocíclica saturada o parcialmente saturada, pero no aromática, la cual comprende de 4 a 7 átomos del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, en donde cada heteroátomo de un heteroarilo o de un heterociclilo se selecciona independientemente a partir de O,

351

N y S.

2. Un compuesto de acuerdo con la reivindicación 1 de la fórmula I:



Fórmula I

o una sal farmacéuticamente aceptable del mismo, en donde:

R^1 es H o alquilo de 1 a 7 átomos de carbono;

R^2 por cada presentación, es independientemente alquilo de 1 a 7 átomos de carbono, halógeno, NO_2, CN, alcanoílo de 1 a 7 átomos de carbono-amino, cicloalquilo de 3 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, $-NR^aR^b$, arilo de 6 a 10 átomos de carbono, heteroarilo o heterociclilo; en donde R^a y R^b por cada presentación, son independientemente H o alquilo de 1 a 7 átomos de carbono;

R^3 es A^1-$C(O)X^1$ o A^2-R^4;

R^4 es arilo de 6 a 10 átomos de carbono, o un heteroarilo, el cual puede ser monocíclico o bicíclico, y el cual puede estar opcionalmente sustituido con uno o más sustituyentes

seleccionados independientemente a partir del grupo que consiste en hidroxilo, hidroxi-alquilo de 1 a 7 átomos de carbono, amino, C(O)-O-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, heteroarilo, -$NHSO_2$-alquilo de 1 a 7 átomos de carbono y bencilo; o R^4 es un heterociclilo, el cual puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en oxo, hidroxilo, hidroxi-alquilo de 1 a 7 átomos de carbono, amino, C(O)-O-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, heteroarilo, -$NHSO_2$-alquilo de 1 a 7 átomos de carbono y bencilo;

R^5 es H, halógeno, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, o halo-alquilo de 1 a 7 átomos de carbono; y

X y X^1 son independientemente OH, -O-alquilo de 1 a 7 átomos de carbono, NR^aR^b, u -O-arilo de 6 a 10 átomos de carbono; en donde el alquilo está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en arilo de 6 a 10 átomos de carbono, heteroarilo, heterociclilo, $C(O)NH_2$, C(O)NH-alquilo de 1 a 6 átomos de carbono, y C(O)N(alquilo de 1 a 6 átomos de carbono)$_2$;

B^1 es –C(O)NH- o –NHC(O)-;

A^1 es un enlace o un alquileno de 1 a 7 átomos de carbono lineal o ramificado, que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno, cicloalquilo de 3 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, y O-acetato; en donde dos grupos alquilo geminales pueden combinarse opcionalmente para formar un cicloalquilo de 3 a 7 átomos de carbono; o

A^1 es un fenilo o un heteroarilo; cada uno de los cuales está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, $-NR^aR^b$, $-OCH_2CO_2H$, y $-OCH_2C(O)NH_2$; o

A^1 es un cicloalquilo de 3 a 7 átomos de carbono;

A^1 es -alquileno de 1 a 4 átomos de carbono-arilo de 6 a 10 átomos de carbono-, -alquileno de 1 a 4 átomos de carbono-heteroaril-, o -alquileno de 1 a 4 átomos de carbono-heterociclil-, en donde A^1 puede estar en cualquier dirección; y

A^2 es un enlace o un alquileno de 1 a 7 átomos de carbono lineal o ramificado, que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, O-acetato, y cicloalquilo de 3 a 7 átomos de

carbono;

n es 0, 1, 2, 3, 4 ó 5;

en donde cada heteroarilo es un anillo aromático monocíclico o bicíclico que comprende de 5 a 10 átomos del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, y

cada heterociclilo es una fracción monocíclica saturada o parcialmente saturada, pero no aromática, la cual comprende de 4 a 7 átomos del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, en donde cada heteroátomo de un heteroarilo o de un heterociclilo se selecciona independientemente a partir de O, N y S.

3. El compuesto de la reivindicación 1 ó 2, en donde:

R^1 es H o alquilo de 1 a 7 átomos de carbono;

R^2 por cada presentación, es independientemente alquilo de 1 a 7 átomos de carbono, halógeno, cicloalquilo de 3 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, haloalquilo de 1 a 7 átomos de carbono, $-NR^aR^b$, arilo de 6 a 20 átomos de carbono, heteroarilo o heterociclilo; en donde R^a y R^b por cada presentación, son independientemente H o alquilo de 1 a 7 átomos de carbono;

R^3 es A^1-$C(O)X^1$ o A^2-R^4;

R^4 es arilo de 6 a 20 átomos de carbono o un heteroarilo, cada uno de los cuales puede ser monocíclico o bicíclico, y cada uno de los cuales puede estar opcionalmente sustituido con uno o más

sustituyentes seleccionados independientemente a partir del grupo que consiste en hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, arilo de 6 a 10 átomos de carbono, heteroarilo, $-NHSO_2$-alquilo de 1 a 7 átomos de carbono y bencilo;

R^5 es H; y

X y X^1 son independientemente OH, -O-alquilo de 1 a 7 átomos de carbono o NR^aR^b;

B^1 es –C(O)NH- o –NHC(O)-;

A^1 es un alquileno de 1 a 7 átomos de carbono lineal o ramificado, que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno, cicloalquilo de 3 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, y O-acetato; en donde dos grupos alquilo geminales pueden combinarse opcionalmente para formar un cicloalquilo de 3 a 7 átomos de carbono; o

A^1 es un fenilo o un heteroarilo; cada uno de los cuales está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, halógeno, $-NR^aR^b$, $-OCH_2CO_2H$, y $-OCH_2C(O)NH_2$; y

A^2 es un enlace o un alquileno de 1 a 7 átomos de

carbono lineal o ramificado, que está opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en halógeno, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, O-acetato, y cicloalquilo de 3 a 7 átomos de carbono; y

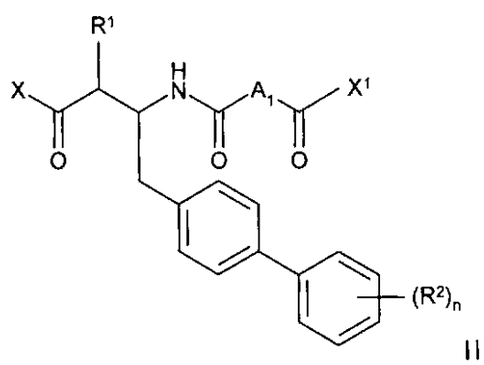
n es 0, 1, 2, 3, 4 ó 5;

en donde cada heteroarilo es un anillo aromático monocíclico o bicíclico que comprende de 5 a 10 átomos del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, y

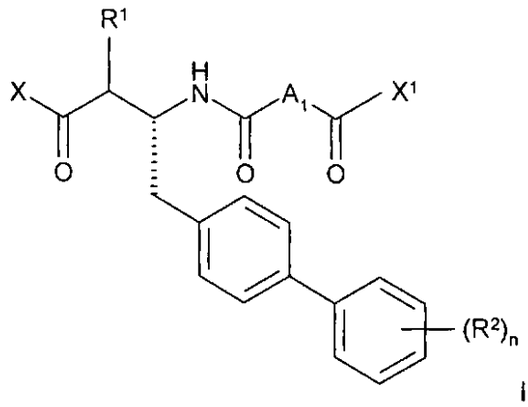
cada heterociclilo es una fracción monocíclica saturada o parcialmente saturada, pero no aromática, la cual comprende de 4 a 7 átomos del anillo seleccionados a partir de átomos de carbono, y de 1 a 5 heteroátomos, en donde cada heteroátomo de un heteroarilo o de un heterociclilo se selecciona independientemente a partir de O, N y S,

o una sal farmacéuticamente aceptable del mismo.

4. El compuesto de acuerdo con la reivindicación 1, 2 ó 3, que tiene fórmula II o IIA:



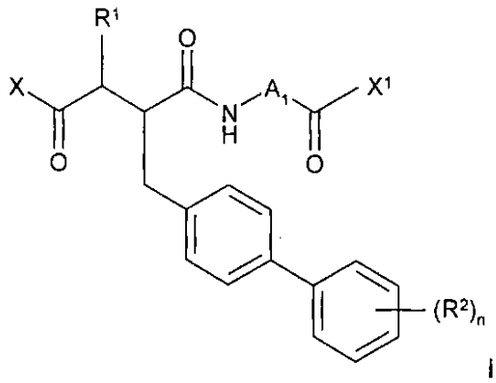
II



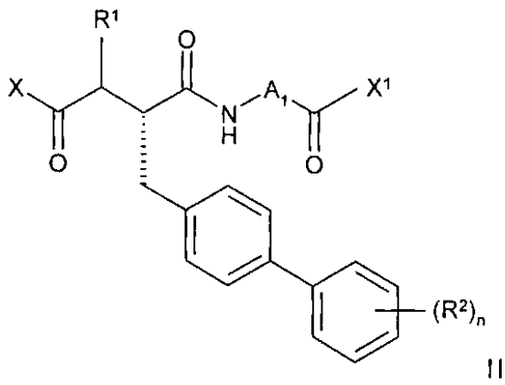
IIA

o una sal farmacéuticamente aceptable del mismo.

5. El compuesto de la reivindicación 1, 2 ó 3, que tiene fórmula III o IIIA:



III



IIIA

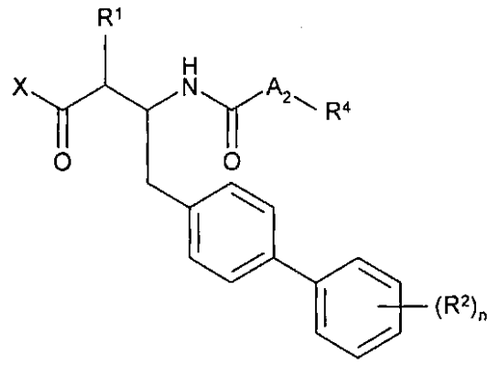
o una sal farmacéuticamente aceptable del mismo.

6. El compuesto de cualquiera de las reivindicaciones 1 a 5, en donde $\mathbf{A^1}$ es un alquileno de 1 a 7 átomos de carbono lineal o ramificado, opcionalmente sustituido, o una sal farmacéuticamente aceptable del mismo.

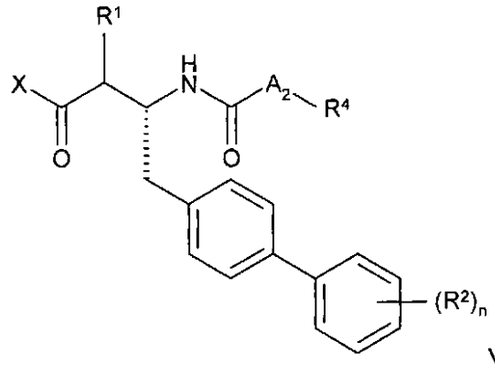
7 El compuesto de cualquiera de las reivindicaciones 1 a 6, en donde $\mathbf{A^1}$ es CH_2CH_2, o una sal farmacéuticamente aceptable del mismo.

8. El compuesto de cualquiera de las reivindicaciones 1 a 5, en donde $\mathbf{A^1}$ es un fenilo o heteroarilo opcionalmente sustituido, o una sal farmacéuticamente aceptable del mismo.

9. El compuesto de la reivindicación 1, 2 ó 3, que tiene fórmula VII o VIIA:



VII



VIIA

o una sal farmacéuticamente aceptable del mismo.

10. El compuesto de la reivindicación 9, en donde A^2 es un enlace o CH_2 o CH_2-CH_2, o una sal farmacéuticamente aceptable del mismo.

11. El compuesto de cualquiera de las reivindicaciones 1 a 10, en donde R^1 es H, R^2 es independientemente halógeno, alcoxilo de 1 a 7 átomos de carbono, hidroxilo, alquilo de 1 a 7 átomos de carbono, o halo-alquilo de 1 a 7 átomos de carbono, n es 0, 1 ó 2, y X y X^1 son independientemente OH u -O-alquilo de 1 a 7 átomos de carbono, o una sal farmacéuticamente aceptable del mismo.

12. El compuesto de cualquiera de reivindicaciones 1 a 11, en donde n es 1 ó 2; R^2 es meta-cloro o meta-fluoro, y el otro grupo R^2 opcional es halógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, y alcoxilo de 1 a 7 átomos de carbono, o una sal farmacéuticamente aceptable del mismo.

13. Una composición farmacéutica, la cual comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 12, o una sal farmacéuticamente aceptable del mismo, y uno o más vehículos farmacéuticamente aceptables.

14. Una combinación que comprende: un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 12, o una sal farmacéuticamente aceptable del mismo, y uno o más agentes terapéuticamente activos seleccionados a partir de un inhibidor de HMG-Co-A-reductasa, un bloqueador de los receptores de

angiotensina, un inhibidor de la enzima convertidora de angiotensina, un bloqueador del canal de calcio, un antagonista de endotelina, un inhibidor de renina, un diurético, un mimético de ApoA-I, un agente anti-diabético, un agente reductor de la obesidad, un bloqueador de los receptores de aldosterona, un bloqueador de los receptores de endotelina, un inhibidor de sintasa de aldosterona, un inhibidor de CETP, y un inhibidor de fosfodiesterasa tipo 5 (PDE5).

15. Un método para inhibir la actividad de la endopeptidasa neutra EC. 3.4. 24.11. en un sujeto que lo necesite, el cual comprende: administrar al sujeto una cantidad terapéuticamente efectiva del compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 12, o una sal farmacéuticamente aceptable del mismo.

16. El método de acuerdo con la reivindicación 15, en donde el trastorno o la enfermedad se selecciona a partir de hipertensión, hipertensión pulmonar, hipertensión sistólica aislada, hipertensión resistente, enfermedad vascular periférica, insuficiencia cardíaca, insuficiencia cardíaca congestiva, hipertrofia de ventrículo izquierdo, angina, insuficiencia renal, falla renal, nefropatía diabética, nefropatía no diabética, síndrome nefrótico, glomerulonefritis, esclerodermia, esclerosis glomerular, proteinuria de enfermedad renal primaria, hipertensión vascular renal, retinopatía diabética y enfermedad renal en etapa final (ESRD), disfunción endotelial, disfunción diastólica, cardiomiopatía hipertrófica, miopatía cardíaca diabética, arritmias supraventriculares y ventriculares, fibrilación

auricular (AF), fibrosis cardíaca, flúter auricular, remodelación vascular perjudicial, estabilización de placa, infarto de miocardio (MI), fibrosis renal, enfermedad de riñón poliquístico (PKD), hipertensión arterial pulmonar, insuficiencia renal, edema cíclico, enfermedad de Menières, hiperaldosteronismo, hipercalciuria, ascitas, glaucoma, trastornos menstruales, parto a pretérmino, pre-eclampsia, endometriosis y trastornos reproductivos, asma, apnea obstructiva del sueño, inflamación, leucemia, dolor, epilepsia, trastornos afectivos, depresión, condición psicótica, demencia, confusión geriátrica, obesidad y trastornos gastrointestinales, sanado de heridas, choque séptico, disfunción de secreción de ácido gástrico, hiperreninemia, fibrosis quística, restenosis, diabetes tipo 2, síndrome metabólico, complicaciones diabéticas, ateroesclerosis, disfunción sexual masculina y femenina.

17. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 12, o una sal farmacéuticamente aceptable del mismo, para utilizarse como un medicamento.

18. El uso del compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 12, o de una sal farmacéuticamente aceptable del mismo, para el tratamiento de un trastorno o enfermedad asociada con la actividad de la endopeptidasa neutra EC. 3.4. 24.11. en un sujeto que necesite dicho tratamiento.

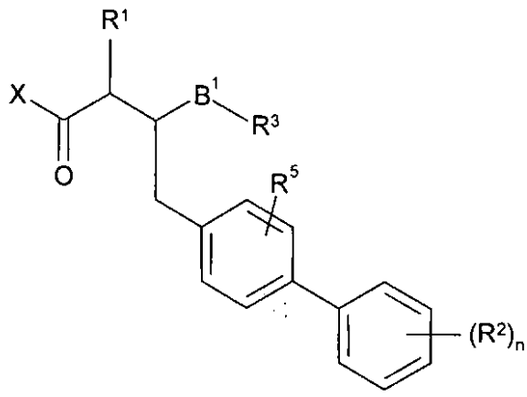
19. El uso de la reivindicación 18, en donde el trastorno o la enfermedad se selecciona a partir de hipertensión, hipertensión pulmonar, hipertensión sistólica aislada, hipertensión resistente,

enfermedad vascular periférica, insuficiencia cardíaca, insuficiencia cardíaca congestiva, hipertrofia de ventrículo izquierdo, angina, insuficiencia renal, falla renal, nefropatía diabética, nefropatía no diabética, síndrome nefrótico, glomerulonefritis, esclerodermia, esclerosis glomerular, proteinuria de enfermedad renal primaria, hipertensión vascular renal, retinopatía diabética y enfermedad renal en etapa final (ESRD), disfunción endotelial, disfunción diastólica, cardiomiopatía hipertrófica, miopatía cardíaca diabética, arritmias supraventriculares y ventriculares, fibrilación auricular (AF), fibrosis cardíaca, flúter auricular, remodelación vascular perjudicial, estabilización de placa, infarto de miocardio (MI), fibrosis renal, enfermedad de riñón poliquístico (PKD), hipertensión arterial pulmonar, insuficiencia renal, edema cíclico, enfermedad de Menières, hiperaldosteronismo, hipercalciuria, ascitas, glaucoma, trastornos menstruales, parto a pretérmino, pre-eclampsia, endometriosis y trastornos reproductivos, asma, apnea obstructiva del sueño, inflamación, leucemia, dolor, epilepsia, trastornos afectivos, depresión, condición psicótica, demencia, confusión geriátrica, obesidad y trastornos gastrointestinales, sanado de heridas, choque séptico, disfunción de secreción de ácido gástrico, hiperreninemia, fibrosis quística, restenosis, diabetes tipo 2, síndrome metabólico, complicaciones diabéticas, ateroesclerosis, disfunción sexual masculina y femenina.

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RESUMEN

La presente invención proporciona un compuesto de la fórmula I';



Fórmula I'

o una sal farmacéuticamente aceptable del mismo, en donde R^1, R^2, R^3, R^5, B^1, X y n se definen en la presente. La invención también se refiere a un método para la elaboración de los compuestos de la invención, y a sus usos terapéuticos. La presente invención proporciona además una combinación de agentes farmacológicamente activos y una composición farmacéutica.

* * * * *

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TRATADO DE COOPERACION EN MATERIA DE PATENTES

TCP

NOTIFICACION DEL REGISTRO DE UN CAMBIO

(Regla 92bis.1 del TCP e Instrucciones Administrativas, Sección 422)

De la OFICINA INTERNACIONAL

Para:

VOEGELI-LANGE, Regina
Novartis Pharma AG
Departamento de Patentes
CH-4002 Basilea
SUIZA

Fecha de envío por correo (día/mes/año):
26 de Mayo de 2011 (26.05.2011)

Referencia de expediente del solicitante o agente:
53601-WO-PCT

NOTIFICACION IMPORTANTE

Solicitud Internacional No.
PCT/EP2010/057247

Fecha de presentación internacional (día/mes/año):
26 de Mayo de 2010 (27.05.2010)

1. Las siguientes indicaciones aparecieron en el registro con respecto a:
( ) el solicitante.
( ) el inventor.
( ) el agente.
( ) el representante general.

Nombre y Dirección:	País de Nacionalidad:	País de Residencia:
	Teléfono No.	
	Facsímil No.	
	Teleimpresor No.	
	Dirección de Correo Electrónico:	

2. La Oficina Internacional notifica mediante la presente a la solicitante que se ha registrado el siguiente cambio con respecto a:
(X) la persona.
( ) el nombre.
( ) la dirección.
( ) la nacionalidad.
( ) la residencia.

Nombre y Dirección:	País de Nacionalidad:	País de Residencia:
SUN, Robert Novartis Institutes for BioMedical Research, Inc. 100 Technology Square Cambridge, Massachusetts 02139 Estados Unidos de América	US	US
	Teléfono No.	
	Facsímil No.	
	Teleimpresor No.	
	Dirección de Correo Electrónico: ( ) Notificaciones por correo eletrónico autorizadas	

3. Otras observaciones, si son necesarias:

Cambio de Estado: La persona identificada en el Recuadro 2 está ahora registrada como solicitante para US solamente y como inventor para todos los Estados (Países) designados.

4. Se ha enviado una copia de esta notificación a:
(X) la Oficina receptora.
( ) la Autoridad de Búsqueda Internacional.
( ) la Autoridad Examinadora Preliminar Internacional.
(X) las Oficinas designadas concernidas.
( ) las Oficinas elegidas concernidas.
( ) otra:

La Oficina Internacional de OMPI 34, chemin des Colombettes 1211 Ginebra 20, Suiza Facsímil No. +41 22 338 89 75	Funcionario autorizado **Righetto Norbert** e-mail: pt05.pct@wipo.int Teléfono No. +41 22 338 74 05

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PATENT COOPERATION TREATY PCT/EP2010/057247

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

VOEGELI-LANGE, Regina
Novartis Pharma AG
Patent Department
CH-4002 Basel
SUISSE

Date of mailing *(day/month/year)*
26 May 2011 (26.05.2011)

Applicant's or agent's file reference
53601-WO-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP2010/057247

International filing date *(day/month/year)*
26 May 2010 (26.05.2010)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
SUN, Robert Novartis Institutes for BioMedical Research, Inc. 100 Technology Square Cambridge, Massachusetts 02139 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:
The person identified in Box 2 is now recorded as applicant for US only and inventor for all designated States.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Righetto Norbert
Facsimile No. +41 22 338 89 75	e-mail pt05.pct@wipo.int Telephone No. +41 22 338 74 05

Form PCT/IB/306 (January 2009) 1/TQP2FTAA0

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 53601-WO-PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2010/057247	International filing date *(day/month/year)* 26 May 2010 (26.05.2010)	Priority date *(day/month/year)* 28 May 2009 (28.05.2009)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant NOVARTIS AG		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 29 November 2011 (29.11.2011)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yolaine Cussac e-mail: pt05.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2010/057247	26.05.2010	28.05.2009

International Patent Classification (IPC) or both national classification and IPC
INV. C07D213/82 C07D239/36 C07D261/18 C07D271/06 C07C233/47 A61K31/21 A61K31/435

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Voyiazoglou, D Telephone No. +31 70 340-3355

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2010/057247

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ 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)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	5-10, 12
	No:	Claims	1-4, 11, 13-19
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Claims 15,16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable claims to the use of a compound in medical treatment, but may allow, however, claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Reference is made to the following document:
D1 : DATABASE WPI Week 199227Thomson Scientific, London, GB; AN 1992-223453& JP 4 149166 A (NIPPON KAYAKU KK) 22 May 1992 (1992-05-22)

1 INDEPENDENT CLAIM 1

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.None of the prior art documents discloses compounds which are part of the formula I' mentioned in claim 1.
However, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not inventive in the sense of Article 33(3) PCT. The problem to be solved is to provide alternative biphenyl compounds as medicaments.
Document D1 discloses biphenyl compounds as medicaments. One of them is biphenyl-4-butanoic acid,((1,1-dimethylethoxy)carbonylamino)-.alpha.hydroxy-, (alpha,beta)-.This compound differs form the claimed compounds in that there is a simpler substituent (no carbonyl group attached between NHC(O) and X1) attached to the NHCO group (for the case where in the structure of formula I' B1 is NHCO R3 is A1C(O)X1, A1 is a bond, and X1 is OBu-t).Having seen the structure of D1 the skilled person would derive to the compounds of the present application without the exercise of inventive skill. Modifying the substituent next to the carbonyl is a common practise in the field of organic chemistry. This is particularly true since it is not expected that modifying such a substituent would have a major impact on the properties of the molecule.

2 INDEPENDENT CLAIMS 13-19

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 13-19 is not inventive in the sense of Article 33(2) PCT.

Document D1 discloses medicaments having very similar structure (see argumentation above). The same reasoning which has already been applied for the inventive step of claim 1, applies, mutatis mutandis, to the subject -matter of the corresponding independent claims 13-19 which therefore is also considered not inventive with respect to D1.

3 DEPENDENT CLAIMS 2-12

Dependent claims 2-4,11 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT).

Dependent claims 5-10,12 contain features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT).

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2010/057247	26.05.2010	28.05.2009

International Patent Classification (IPC) or both national classification and IPC
INV. C07D213/82 C07D239/36 C07D261/18 C07D271/06 C07C233/47 A61K31/21 A61K31/435

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Voyiazoglou, D Telephone No. +31 70 340-3355

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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.
53601-WO-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2010/057247	26/05/2010	28/05/2009
Applicant		
NOVARTIS AG		

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 4 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. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/057247

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/82 C07D239/36 C07D261/18 C07D271/06 C07C233/47
A61K31/21 A61K31/435
ADD.
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 C07C A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 199227 Thomson Scientific, London, GB; AN 1992-223453 XP002591646 & JP 4 149166 A (NIPPON KAYAKU KK) 22 May 1992 (1992-05-22)	1-4,11, 13-19
A	* abstract compound with RN:144139-09-3	5-10,12
A	GB 2 037 754 A (NIPPON KAYAKU KK) 16 July 1980 (1980-07-16) line 1 - page 15, line 10	1-19
A	EP 0 497 192 A2 (HOFFMANN LA ROCHE [CH]) 5 August 1992 (1992-08-05) page 46; claims 1,8	1-19

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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
13 July 2010	23/07/2010

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, Fax: (+31-70) 340-3016	Voyiazoglou, D

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/057247

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	W. YAO ET AL: "Potent P1' biphenylmethyl substituted aggrecanase inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 12, 2002, pages 101-104, XP002591647 Pergamon, Elsevier Science ISSN: 0960-894X table 1	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/057247

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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GB 2037754 A	16-07-1980	AR 227636 A1	30-11-1982
		AU 530362 B2	14-07-1983
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		NZ 241409 A	27-06-1994
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		US 5304549 A	19-04-1994

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-165101- -00000-0000

Fecha: 2011-11-30 16:58:17 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 364

Act. 411 PRESENTACION Folios: 405

PATENTE DE INVENCIÓN ☐ MODELO DE UT

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ MODELO DE UTILIDAD PCT ☐ **Art.33 Decisión 486/00, Circular Única**

- ☐ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita 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 ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐