Industria y Comercio

SUPERINTENDENCIA

CSA850669

Organizacion y Digitalizacion CSA Ltda

Delegatura de Propiedad Industrial

División de Nuevas Creciones

SUPERINTENDENCIA
INVENTARI

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 08 - 1924

54 **TÍTULO** "INHIBIDORES DE AGRECANASA: GLUTAMATO"

51 **CLASIFICACIÓN INTERNACIONAL**

71 **SOLICITANTE** WYETH

DOMICILIO NUEVA JERSEY, ESTADOS UNIDOS de América

74 **APODERADO** ÁLVARO Correa-Ordoñez T.P.-20 281

22 **BOGOTÁ, D. C.,** 10 de Enero de 2008

(FORMA P 10)

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-001924- -00000-0000
Fecha: 2008-01-10 16:12:56 Dep: 2020 NUECREACIONI ón
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 776

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

11 Feb 2008

(1) SOLICITUD DE :

[X]	Patente de Invención	[ ]	Patente de Modelo de Utilidad
[ ]	Capítulo I.	[X]	Capítulo II.

(2) SOLICITANTE (71)

Nombre: WYETH
Dirección: Five Giralda Farms, Madison, Nueva Jersey 07940, Estados Unidos de América
Nacionalidad o Domicilio: Nueva Jersey, Estados Unidos de América
Lugar de Constitución: Delaware, Estados Unidos de América
Teléfono: Fax:
E-Mail

IDENTIFICACION
C.E. [ ] Otro [ ]
Cual
Número

(3) REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ
Dirección: Avenida 82 No.10-62 Piso 6
Teléfono: 634 1500 Fax: 376 2211
E-Mail: office.bogota@bakernet.com

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.143.366 de Usaquén TP 20.281

(4) INVENTOR (ES) (72)

Nombre: SUM, Phaik-Eng; HOW, David, Brian; SABATINI, Joshua, James; XIANG, Jason, Shaoyun; IPEK, Manus y FEYFANT, Eric
Dirección: 16 Chamberlain Court, Pomona, NY 10970, Estados Unidos de América; 10 High Avenue, Nyack, NY 10960, Estados Unidos de América; 12 Old Mamaroneck Road, Apt. 7G, White Plains, NY 10605, Estados Unidos de América; 3 River Street, Winchester, MA 01890, Estados Unidos de América; 197 School Street, Watertown, MA 02472, Estados Unidos de América y 41 Kendall Road, Lexington, MA 02421 Estados Unidos de América, respectivamente
Nacionalidad o Domicilio: Canadiense, Canadiense, Estadounidense, Estadounidense, Estadounidense y Francés

(5) PCT (85)

Solicitud Internacional No. PCT/US2006/027066 Fecha 11-JUL-06
Publicación Internacional No. WO 2007/008994 Fecha 18-ENE-07

(6) Título (54) INHIBIDORES DE AGRECANASA GLUTAMATO

(7) Clasificación Internacional (51) C07C 237/22, C07C 237/42, C07C 235/84, C07C 231/16, C07D 317/58, A61K 31/166, C07D 333/24, A61K 31/36, C07D 213/56, A61K 31/381, C07D 277/30, A61K31/4409, C07C 323/41, A61K 31/426, C07C 259/06

(8) Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	11-JUL-05	60/697,590

(9) Comprobante de pago No. 07-99185 y 08-1173 **Fecha** 05-Dic-07 y 03-Ene-08

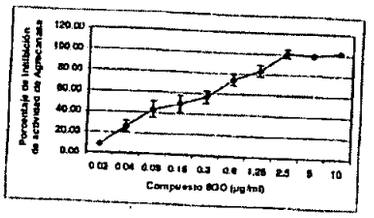
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

(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
- [X] Documento de cesión del inventor al solicitante o a su causante
- [ ] 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
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: Extractos, Reporte de búsqueda y opinión escrita, notificación de presentación de documento de prioridad y nptificación de cambio

(11) **FIGURA CARATERISTICA**

Figura 1: Inhibición de degradación de agrecán mediante compuesto de ensayo 8OO



(12) Solicito la concesión de la patente.

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

RECIBO DE PAGO

3

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-001924- -00000-0000

Fecha: 2008-01-10 16:12:56 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 776

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 99,185
FECHA : DICIEMBRE 5 DE 2007

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
RAISBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	71025976	05/12/2007	42,693,000.00

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

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

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

4

2008/001

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 1,173
FECHA : ENERO 3 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-001924- -00000-0000
Fecha: 2008-01-10 16:12:56 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 776

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

DOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	4051023	03/01/2008	12,953,500.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	998	VALOR COMPLEMENTO TARIFA A#O ANTR	19,000.00
			TOTAL : $	19,000.00

SON: DIEZ Y NUEVE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

TRADUCCIÓN OFICIAL N° 090108 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

Traducción de poder otorgado por WYETH con respecto a Solicitud de Patente en Colombia para

INHIBIDORES DE AGRECANASA GLUTAMATO.

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:

   MICHELLE L. MCGOWAN
3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY
4. LLEVA EL SELLO DE MICHELLE L. MCGOWAN, NOTARIO

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY
6. EL 16 DE NOVIEMBRE DE 2007
7. POR Michellene Davis, TESORERO DE NUEVA JERSEY
8. N° A309312
9. SELLO (APARECE ADHERIDO SELLO DORADO)
10. FIRMA (Firma ilegible)

[No se traduce el texto del poder por estar en inglés y en español]

[No se traduce la certificación notarial por estar en inglés y en español]

[Sello que dice: "Michelle L. McGowan, Notario Público, Estado de Nueva Jersey. No. 2108903. Calificado en el Condado de Morris. Comisión vence el 9 de febrero de 2011"]

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Dec 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

TRADUCCIÓN OFICIAL N° 090108 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

---

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 99910

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MICHELLE L MC GOWAN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
MICHELLE L MC GOWAN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 16TH DAY OF NOVEMBER 2007

7. BY: Michellene Davis, NEW JERSEY TREASURER

8. NO. A309312

9. SEAL/STAMP:

10. SIGNATURE

BAKER & McKENZIE

AM102063 Colombia

Raisbeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.068.840-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

POWER OF ATTORNEY

The undersigned.

WYETH

with offices at

Five Giralda Farms, Madison, NJ 07940,
United States of America

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA

all members of the law firm Raisbeck, Lara, Rodriguez & Rueda, with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, and for so long as they remain members of the law firm, a full and sufficient power of attorney with respect to Colombian patent application(s) based on PCT/US2006/027066 and entitled "GLUTAMATE AGGRECANASE INHIBITORS" and to obtain patent protection thereof, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of a patent(s) based upon said patent application(s), including filing of assignments, change of name or address, voluntary cancellation; and defending oppositions, cancellations, nullity, writ mandamus, and in general the civil, penal, an administrative processes relating to those rights.

I hereby ratify all lawful actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 14th day of November of 2007

Signature of the person issuing the Power

WYETH

William H. Calnan
Assistant Secretary

PODER DE ABOGADO

La abajo firmada,

WYETH

con oficinas en

Five Giralda Farms, Madison, NJ 07940,
Estados Unidos de América

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

Todos miembros de la firma de abogados Raisbeck, Lara, Rodríguez & Rueda, con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, y hasta tanto ellos continúen siendo miembros de la firma, poder especial amplio y suficiente con respecto a la solicitud(es) de patente en Colombia basada(s) en PCT/US2006/027066 y titulada "INHIBIDORES DE AGRECANASA GLUTAMATO", y para obtener la protección de patente de la misma, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de la(s) patente(s) de invención basada(s) en la mencionada solicitud de patente, incluyendo presentación de traspasos, cambio de nombre o dirección, cancelación voluntaria; y defensa en oposiciones, cancelaciones, nulidades, la tutela, y en general procesos civiles, penales, administrativos relacionados con estos derechos.

Igualmente, ratifico todo lo actuado en derecho hasta el momento en nombre de esta compañía por cualquiera de los mencionados apoderados en los casos mencionados.

Dado y firmado en

A los 14 días del mes de noviembre de 2007

Firma de la persona que firma el Poder

NOTARIAL CERTIFICATION

On this **14th** day of **November** 2007, the undersigned Notary

CERTIFIES

1. That **William H. Calnan**

set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as

Assistant Secretary

of the judicial person **WYETH**

4. That the judicial person **WYETH** having its home office in
Five Giralda Farms, Madison, NJ 07940,
United States of America

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
Minutes of the Board of Directors Meeting held on April 26, 2007.

Michelle L. McGowan

Notary Public
MICHELLE L. McGOWAN
Notary Public, State of New Jersey
No. 2108903
Qualified in Morris County
Commission Expires Feb. 9, 2011

CERTIFICACION NOTARIAL

A los 14 días del mes de noviembre de 2007, el suscrito Notario

DA FE

1 Que William H. Calnan

suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de
Subsecretario

de la persona jurídica **WYETH**

4 Que la persona jurídica **WYETH** con sede en
Five Giralda Farms, Madison, NJ 07940,
Estados Unidos de América

está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
Actas de la reunión de Junta Directiva celebrada el 26 de abril de 2007.]

El Notario Público

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 January 2007 (18.01.2007)

PCT

(10) International Publication Number
WO 2007/008994 A3

(51) International Patent Classification:
C07C 237/22 (2006.01) *C07C 237/42* (2006.01)
C07C 235/84 (2006.01) *C07C 231/16* (2006.01)
C07D 317/58 (2006.01) *A61K 31/166* (2006.01)
C07D 333/24 (2006.01) *A61K 31/36* (2006.01)
C07D 213/56 (2006.01) *A61K 31/381* (2006.01)
C07D 277/30 (2006.01) *A61K 31/4409* (2006.01)
C07C 323/41 (2006.01) *A61K 31/426* (2006.01)
C07C 259/06 (2006.01)

(21) International Application Number:
PCT/US2006/027066

(22) International Filing Date: 11 July 2006 (11.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/697,590 11 July 2005 (11.07.2005) US

(71) Applicant *(for all designated States except US)*: **WYETH** [US/US]; Five Giralda Farms, Madison, NJ 07940 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SUM, Phaik-Eng** [CA/US]; 16 Chamberlain Court, Pomona, NY 10970 (US). **HOW, David, Brian** [CA/US]; 10 High Avenue, Nyack, NY 10960 (US). **SABATINI, Joshua, James** [US/US]; 3 Old Mamaroneck Road, Apt. #5e, White Plains, NY 106065 (US). **XIANG, Jason, Shaoyun** [US/US]; 3 River Street, Winchester, MA 01890 (US). **IPEK, Manus** [US/US]; 197 School Street, Watertown, MA 02472 (US). **FEYFANT, Eric** [FR/US]; 41 Kendell Road, Lexington, MA 02421 (US).

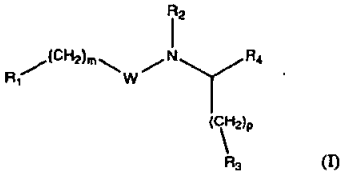
(74) Agent: **SUPERKO, Colleen**; WILMER CUTLER PICKERING HALE AND DORR LLP, 60 State Street, Boston, MA 02109 (US).

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

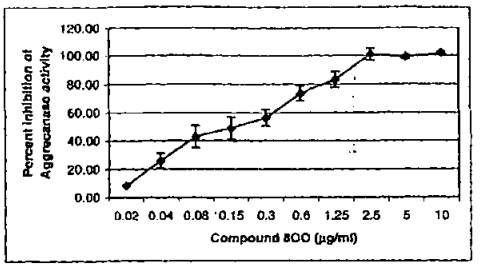
[Continued on next page]

(54) Title: GLUTAMATE AGGRECANASE INHIBITORS



(I)

Inhibition of aggrecan degradation by test compound 800



(57) Abstract: The present invention relates to compounds of the formula (I), which are modulators of metalloproteinase activity. and pharmaceutically acceptable salts thereof, wherein W is -C(O)-, -OC(O)-, -NHC(O)-, -C(O)O-, Or -C(O)NH-; R_1 is phenyl, heteroaryl, biphenyl, bicyciic aryi, tricyclic aryl, bicyclic heteroaryl. or tricyclic heteroaryl, each optionally substituted with one or more of R_5 or R_6, and when Ri is substituted with more than one of R_5 or Re, the substituents can be identical or different; R_2 is hydrogen, (C_1 -C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -$(CH_2)_nR_{11}$, -OH, or -0-(C_1-C_6) alkyl; R_3 is -CO_2H, -$CONH_2$, -CONHOH, -$CONHSO_2R_7$, tetrazole, -SO_2NHR_7, -SO_3H, -$PO(OH)NH_2$, -$PO(OH)OR_7$, -$CONHR_7$, -$COOR_7$, an acid mimetic group, or a 5 or 6-membered heterocycloalkyl or heteroaryl containing 1 to 4 heteroatoms selected from O, N, S; R_4 is -CO_2H, -$CONH_2$, -$(CH_2)_nOR_7$, or -$CONR_9R_{10}$;

WO 2007/008994 A3

GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

(88) Date of publication of the international search report:
12 July 2007

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 January 2007 (18.01.2007)

PCT

(10) International Publication Number
WO 2007/008994 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/US2006/027066

(22) International Filing Date: 11 July 2006 (11.07.2006)

(25) Filing Language: English

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(30) Priority Data:
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(72) Inventors; and

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(74) Agent: **SUPERKO, Colleen**; WILMER CUTLER PICKERING HALE AND DORR LLP, 60 State Street, Boston, MA 02109 (US).

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

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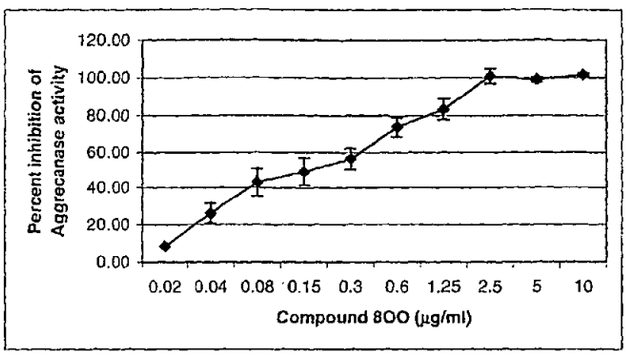
(54) Title: GLUTAMATE AGGRECANASE INHIBITORS

Inhibition of aggrecan degradation by test compound 800



(57) Abstract: The present invention relates to modulators of metalloproteinase activity.

WO 2007/008994 A2

GLUTAMATE AGGRECANASE INHIBITORS

[0001] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein.

[0002] This patent disclosure contains material that is subject to copyright protection. The copyright owner has no objection to the facsimile reproduction by anyone of the patent document or the patent disclosure, as it appears in the U.S. Patent and Trademark Office patent file or records, but otherwise reserves any and all copyright rights whatsoever.

Related Application

[0003] This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 60/697,590 filed on July 11, 2005, which is hereby incorporated by reference herein in its entirety.

Field of the Invention

[0004] The present invention relates to compounds and their use as, for example, metalloproteinase inhibitors.

Background of the Invention

[0005] Metalloproteinases, including matrix metalloproteinases and aggrecanases, are known to have a role in the breakdown of connective tissue. Matrix metalloproteinases ("MMPs") constitute a superfamily of proteolytic enzymes that are genetically related and capable of degrading almost all the constituents of extracellular matrix and basement membrane that restrict cell movement. Aggrecanases are members of the ADAMTS (A disintegrin and metalloproteinase with thrombospondin motifs) family of proteins. Aggrecanase-1 and aggrecanase-2 have been designated ADAMTS-4 and ADAMTS-5, respectively (Tang BL, *Int J Biochem Cell Biol* 2001, 33, 33-44).

[0006] The ADAMTS family is involved in cleaving aggrecan, a cartilage component also known as the large aggregating chondroitin sulphate proteoglycan (Abbaszade I et al., *J Biol Chem* 1999, 274, 23443-23450), procollagen processing

(Colige A et al., *Proc Natl Acad Sci USA* 1997, 94, 2374-2379), angiogenesis (Vazquez F et al., *J Biol Chem* 1999, 274, 23349-23357), inflammation (Kuno K et al., *J Biol Chem* 1997, 272, 556-562) and tumor invasion (Masui T. et al., *J Biol Chem* 1997, 272, 556-562). MMPs have been shown to cleave aggrecan as well.

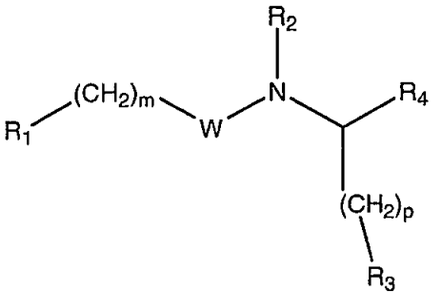
[0007] The loss of aggrecan has been implicated in the degradation of articular cartilage in arthritic diseases, for example osteoarthritis is a debilitating disease which affects at least 30 million Americans. Degradation of articular cartilage and the resulting chronic pain can severely reduce quality of life. An early and important characteristic of the osteoarthritic process is loss of aggrecan from the extracellular matrix, resulting in deficiencies in the biomechanical characteristics of the cartilage. Likewise, MMPs and aggrecanases are known to play a role in many disorders in which extracellular protein degradation or destruction occurs, such as cancer, asthma, chronic obstructive pulmonary disease ("COPD"), atherosclerosis, age-related macular degeneration, myocardial infarction, corneal ulceration and other ocular surface diseases, hepatitis, aortic aneurysms, tendonitis, central nervous system diseases, abnormal wound healing, angiogenesis, restenosis, cirrhosis, multiple sclerosis, glomerulonephritis, graft versus host disease, diabetes, inflammatory bowel disease, shock, invertebral disc degeneration, stroke, osteopenia, and periodontal diseases.

[0008] Therefore, metalloproteinase inhibitors, including inhibitors of MMPs and aggrecanases, are needed.

[0009] The present invention is directed to these and other important ends.

Summary of the Invention

[0010] In one embodiment, the invention provides compounds of the Formula (I):



(I)

and pharmaceutically acceptable salts thereof,

wherein

W is –C(O)-, -OC(O)-, –NHC(O)-, -C(O)O-, or –C(O)NH-;

R_1 is phenyl, heteroaryl, biphenyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each optionally substituted with one or more of R_5 or R_6, and when R_1 is substituted with more than one of R_5 or R_6, the substituents can be identical or different;

R_2 is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -$(CH_2)_nR_{11}$, -OH, or -O-(C_1-C_6) alkyl;

R_3 is -CO_2H, -$CONH_2$, -CONHOH, -$CONHSO_2R_7$, tetrazole, -SO_2NHR_7, -SO_3H, -$PO(OH)NH_2$, -$PO(OH)OR_7$, -$CONHR_7$, -$COOR_7$, an acid mimetic group, or a 5 or 6-membered heterocycloalkyl or heteroaryl containing 1 to 4 heteroatoms selected from O, N, S;

R_4 is -CO_2H, -$CONH_2$, -$(CH_2)_nOR_7$, or -$CONR_9R_{10}$;

R_5 is aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, -CO-(C_1-C_6) alkyl, -CO-aryl, -CO-heteroaryl, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2NH-aryl, -SO_2NH-heteroaryl, -$NHSO_2$-(C_1-C_6) alkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl, -CONH-heteroaryl, (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, or -CONH-(C_3-C_6) cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different;

R_6 and R_{12} are each independently hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$, (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6)

alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_9 and R_{10} are each independently hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkyl-OH, (C_1-C_6) alkyl-O-(C_1-C_6) alkyl, aryl, cycloalkyl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_9 and R_{10} together may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_{11} is aryl, heteroaryl, or cycloalkyl;

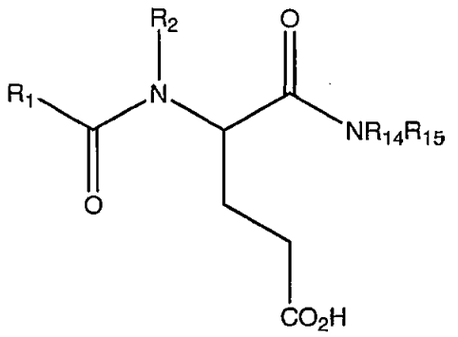
R_{13} is halogen, -O-(C_1-C_6) alkyl, -CO_2H, -OH, -CF_3, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl substituted with -OH, aryl substituted with -NH_2, aryl substituted with -O-(C_1-C_6) alkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl;

m is 0-4;

n is 0-4; and

p is 0-2.

[0011] In another embodiment, the invention provides compounds of the Formula (II):



(II)

and pharmaceutically acceptable salts thereof,

wherein

R_2 is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -$(CH_2)_pR_{11}$, -OH, or -O-(C_1-C_6) alkyl;

R_{14} and R_{15} are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, heterocycloalkyl -$(CH_2)_n$-aryl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_{14} and R_{15} together may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

p is 0-2, and

R_1, R_{11}, R_{12}, and n are as described above for compounds of the Formula (I).

[0012] In another embodiment, the compounds or pharmaceutically acceptable salts of the compounds of Formula (I) or Formula (II) are useful as pharmaceutical compositions comprising compounds or pharmaceutically acceptable salts of compounds of Formula (I) or Formula (II) and a pharmaceutically acceptable carrier.

[0013] In one embodiment, the compounds or pharmaceutically acceptable salts of the compounds of the Formula (I) or Formula (II) are useful as metalloproteinase modulators.

[0014] In one embodiment, the invention provides methods for treating a metalloproteinase-related disorder, comprising administering to an animal in need thereof the compounds or pharmaceutically acceptable salts of compounds of Formula (I) or Formula (II) in an amount effective to treat a metalloproteinase-related disorder.

[0015] In one embodiment, the invention provides methods of synthesizing the compounds or pharmaceutically acceptable salts of compounds of Formula (I) or Formula (II). In another embodiment, the invention provides compounds or pharmaceutically acceptable salts of compounds of Formula (I) or Formula (II) made by particular processes.

Description of the Invention

[0016] All recitations of a group, such as alkyl, are understood for the purposes of this specification to encompass both substituted and unsubstituted forms.

[0017] The term "alkyl", as used herein, whether used alone or as part of another group, refers to a substituted or unsubstituted aliphatic hydrocarbon chain and includes, but is not limited to, straight and branched chains containing from 1 to 12 carbon atoms, or in some instances, from 1 to 6 carbon atoms, unless explicitly specified otherwise. For example, methyl, ethyl, propyl, isopropyl, butyl, i-butyl and t-butyl are encompassed by the term "alkyl." $(C_1\text{-}C_6)$-alkyl includes straight and branched chain aliphatic groups having from 1 to 6 carbons. Specifically included within the definition of "alkyl" are those aliphatic hydrocarbon chains that are optionally substituted. The alkyl may suitably be a $(C_1\text{-}C_3)$-alkyl. In one embodiment, an alkyl is optionally substituted with one or more of the following groups: -halogen, $-N(R')_2$, methylenedioxo, ethylenedioxo, $-NHSO_2R'$, -NR'COR', $-NHCO_2R'$, $-NO_2$, $-SO_2N(R')_2$, $-SO_2R'$, -OR', -COR', $-CO_2R'$, $-CON(R')_2$, or -CN, wherein each R' is independently hydrogen, unsubstituted $(C_1\text{-}C_6)$-alkyl, or unsubstituted aryl.

[0018] The carbon number as used in the definitions herein refers to carbon backbone and carbon branching, but does not include carbon atoms of the substituents, such as alkoxy substitutions and the like.

[0019] The term "alkenyl", as used herein, whether used alone or as part of another group, refers to a substituted or unsubstituted hydrocarbon chain and includes, but is not limited to, straight and branched chains having 2 to 8 carbon atoms e.g. 2 to 6 carbon atoms and containing at least one double bond. In one embodiment, the alkenyl moiety has 1 or 2 double bonds. Such alkenyl moieties may exist in the E or Z conformations and the compounds of this invention include both conformations. $(C_2\text{-}C_6)$ alkenyl includes a 2 to 6 carbon straight or branched chain having at least one carbon-carbon double bond. Specifically included within the definition of "alkenyl" are those

aliphatic hydrocarbon chains that are optionally substituted. In one embodiment, a heteroatom, such as O, S or N, attached to an alkenyl is not attached to a carbon atom that is bonded to a double bond. In one embodiment, an alkenyl is optionally substituted with one or more of the following groups: -halogen, $-N(R')_2$, methylenedioxo, ethylenedioxo, $-NHSO_2R'$, -NR'COR', $-NHCO_2R'$, $-NO_2$, $-SO_2N(R')_2$, $-SO_2R'$, -OR', -COR', $-CO_2R'$, $-CON(R')_2$, or -CN, wherein each R' is independently hydrogen, unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl.

[0020] The term "alkynyl", as used herein, whether used alone or as part of another group, refers to a hydrocarbon moiety containing at least one carbon-carbon triple bond. (C_2-C_6) alkynyl includes a 2 to 6 carbon straight or branched chain having at least one carbon-carbon triple bond. In one embodiment, an alkynyl is optionally substituted with one or more of the following groups: -halogen, $-N(R')_2$, methylenedioxo, ethylenedioxo, $-NHSO_2R'$, -NR'COR', $-NHCO_2R'$, $-NO_2$, $-SO_2N(R')_2$, $-SO_2R'$, -OR', -COR', $-CO_2R'$, $-CON(R')_2$, or -CN, wherein each R' is independently hydrogen, unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl.

[0021] The term "cycloalkyl" refers to a monocyclic, bicyclic, tricyclic, fused, bridged, or spiro monovalent saturated or unsaturated non-aromatichydrocarbon ring system of 3-15 carbon atoms e.g. 3 to 6 carbon atoms. Any suitable ring position of the cycloalkyl moiety may be covalently linked to the defined chemical structure. Examples of cycloalkyl moieties include, but are not limited to, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, spiro[4.5]decanyl, and homologs, isomers, and the like. C_3-C_6 cycloalkyl includes monocyclic, saturated rings of 3 to 6 carbons. In one embodiment, a cycloalkyl is optionally substituted with one or more of the following groups: -V-halogen, $-(C_1-C_6)$-alkyl, $-(C_2-C_6)$-alkenyl, $-(C_2-C_6)$-alkynyl, $-V-N(R')_2$, methylenedioxo, ethylenedioxo, $-V-NHSO_2R'$, -V-NR'COR', $-V-NHCO_2R'$, $-V-NO_2$, $-V-SO_2N(R')_2$, $-V-SO_2R'$, -V-OR', -V-COR', $-V-CO_2R'$, $-V-CON(R')_2$, or –V-CN, wherein each R' is independently hydrogen, unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl; and wherein each V is independently a bond or (C_1-C_6)-alkyl. Cycloalkylalkyl when used herein refers to a (C_1-C_6)-alkyl group as defined above substituted by a C_3 to C_{15} cycloalkyl group as defined above, e.g. cyclohexylmethyl and cyclohexylethyl.

[0022] "Heteroaryl" refers to a 5 to 6 membered aromatic heterocyclic ring which contains from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur atoms in the ring, and to which may be fused with a carbocyclic or heterocyclic ring at any possible position (e.g. fused to one or more carbocyclic or heterocyclic rings, each having 5-8 ring atoms, the fused heterocyclic ring containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur atoms in the ring), e.g. it is suitably a bicyclic or tricyclic ring. Exemplary heteroaryl groups include, but are not limited to, furanyl, furazanyl, homopiperazinyl, imidazolinyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrimidinyl, phenanthridinyl, pyranyl, pyrazinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolinyl, thiadiazinyl, thiadiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, and triazolyl. In one embodiment, a heteroaryl is optionally substituted with one or more of the following groups: -V-halogen, -(C_1-C_6)-alkyl, -(C_2-C_6)-alkenyl, -(C_2-C_6)-alkynyl, -V-N(R')$_2$, methylenedioxo, ethylenedioxo, -V-NHSO$_2$R', -V-NR'COR', -V-NHCO$_2$R', -V-NO$_2$, -V-SO$_2$N(R')$_2$, -V-SO$_2$R', -V-OR', -V-COR', -V-CO$_2$R', -V-CON(R')$_2$, or –V-CN, wherein each R' is independently hydrogen, unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl; and wherein each V is independently a bond or (C_1-C_6)-alkyl.

[0023] "Heterocycloalkyl" refers to a 5 to 7-membered saturated or unsaturated nonaromatic ring containing carbon atoms and from 1 to 4 heteroatoms selected from N, O, and S which may suitably be monocylic or may be fused to one or more further rings to provide a polycyclic moiety e.g. a bicyclic or tricyclic moiety. The further ring(s) may be carbocyclic rings(s) or they may contain from 1 to 4 further heteroatoms selected from N, O and S, preferably they are carbocyclic rings. The further ring(s) may be saturated, unsaturated or aromatic rings(s), preferably they are non-aromatic rings. Exemplary heterocycloalkyl groups include, but are not limited to, azepanyl, azetidinyl, aziridinyl, imidazolidinyl, morpholinyl, oxazolidinyl, oxazolidinyl, piperazinyl, piperidinyl, pyrazolidinyl, pyrrolidinyl, quinuclidinyl, tetrahydrofuranyl, and thiomorpholinyl. In one embodiment, a heterocycloalkyl is optionally substituted with one or more of the following: -V-halogen, -(C_1-C_6)-alkyl, -(C_2-C_6)-alkenyl, -(C_2-C_6)-alkynyl, -V-N(R')$_2$, methylenedioxo, ethylenedioxo, -V-NHSO$_2$R', -V-NR'COR', -V-NHCO$_2$R', -V-NO$_2$, -V-SO$_2$N(R')$_2$, -V-SO$_2$R', -V-OR', -V-COR', -V-CO$_2$R', -V-CON(R')$_2$, or –V-CN,

wherein each R' is independently hydrogen, unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl; and wherein each V is independently a bond or (C_1-C_6)-alkyl.

[0024] The term " aryl" as used herein as a group or part of a group refers to an aromatic carbocyclic ring system, e.g., of from 6 to 14 carbon atoms such as phenyl, which may be optionally substituted. An aryl group may be fused with a carbocyclic or heterocyclic ring at any possible position (e.g. fused to one or more carbocyclic or heterocyclic rings, each having 5-8 ring atoms, the fused heterocyclic ring containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur atoms in the ring). "Phenyl", as used herein, whether used alone or as part of another group, refers to a substituted or unsubstituted phenyl group. The aryl fused with a carbocyclic ring may suitably be a bicyclic aryl or a tricyclic aryl. In one embodiment, an aryl group such as phenyl is optionally substituted with one or more of the following: -V-halogen, -(C_1-C_6)-alkyl, -(C_2-C_6)-alkenyl, -(C_2-C_6)-alkynyl, -V-N(R')$_2$, methylenedioxo, ethylenedioxo, -V-NHSO$_2$R', -V-NR'COR', -V-NHCO$_2$R', -V-NO$_2$, -V-SO$_2$N(R')$_2$, -V-SO$_2$R', -V-OR', -V-COR', -V-CO$_2$R', -V-CON(R')$_2$, or –V-CN, wherein each R' is independently hydrogen, unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl; and wherein each V is independently a bond or (C_1-C_6)-alkyl.

[0025] The term "biphenyl" as used herein refers to two phenyl groups connected at one carbon site on each ring. In one embodiment, one or both phenyl groups is independently optionally substituted with one or more of the following groups: -V-halogen, -(C_1-C_6)-alkyl, -(C_2-C_6)-alkenyl, -(C_2-C_6)-alkynyl, -V-N(R')$_2$, methylenedioxo, ethylenedioxo, -V-NHSO$_2$R', -V-NR'COR', -V-NHCO$_2$R', -V-NO$_2$, -V-SO$_2$N(R')$_2$, -V-SO$_2$R', -V-OR', -V-COR', -V-CO$_2$R', -V-CON(R')$_2$, or –V-CN, wherein each R' is independently hydrogen, unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl; and wherein each V is independently a bond or (C_1-C_6)-alkyl.

[0026] The term "biaryl" as used herein refers to two aryl groups connected at one carbon site on each ring. In one embodiment, one or both aryl groups is independently optionally substituted with one or more of the following groups: -V-halogen, -(C_1-C_6)-alkyl, -(C_2-C_6)-alkenyl, -(C_2-C_6)-alkynyl, -V-N(R')$_2$, methylenedioxo, ethylenedioxo, -V-NHSO$_2$R', -V-NR'COR', -V-NHCO$_2$R', -V-NO$_2$, -V-SO$_2$N(R')$_2$, -V-SO$_2$R', -V-OR', -V-COR', -V-CO$_2$R', -V-CON(R')$_2$, or –V-CN, wherein each R' is independently hydrogen,

unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl; and wherein each V is independently a bond or (C_1-C_6)-alkyl.

[0027] The term "bicyclic aryl" as used herein refers to two fused carbocyclic groups, wherein one or both of the carbocyclic groups is aromatic. For example, a bicyclic aryl can contain from 8 to 12 ring atoms. In one embodiment, one or both carbocyclic groups of the bicyclic aryl is independently optionally substituted with one or more of the following groups: -V-halogen, -(C_1-C_6)-alkyl, -(C_2-C_6)-alkenyl, -(C_2-C_6)-alkynyl, - V-N(R')$_2$, methylenedioxo, ethylenedioxo, -V-NHSO$_2$R', -V-NR'COR', -V-NHCO$_2$R', -V-NO$_2$, -V-SO$_2$N(R')$_2$, -V-SO$_2$R', -V-OR', -V-COR', -V-CO$_2$R', -V-CON(R')$_2$, or –V-CN, wherein each R' is independently hydrogen, unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl; and wherein each V is independently a bond or (C_1-C_6)-alkyl.

[0028] The term "tricyclic aryl" as used herein refers to three fused carbocyclic groups, wherein two or three of the carbocyclic groups is aromatic. For example, a tricyclic aryl can contain from 13 to 18 ring atoms. In one embodiment, one or more of the carbocyclic groups of the tricyclic aryl are independently optionally substituted with one or more of the following groups: -V-halogen, -(C_1-C_6)-alkyl, -(C_2-C_6)-alkenyl, -(C_2-C_6)-alkynyl, - V-N(R')$_2$, methylenedioxo, ethylenedioxo, -V-NHSO$_2$R', -V-NR'COR', -V-NHCO$_2$R', -V-NO$_2$, -V-SO$_2$N(R')$_2$, -V-SO$_2$R', -V-OR', -V-COR', -V-CO$_2$R', -V-CON(R')$_2$, or –V-CN, wherein each R' is independently hydrogen, unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl; and wherein each V is independently a bond or (C_1-C_6)-alkyl.

[0029] The term "bicyclic heteroaryl" as used herein refers to two fused cyclic groups, wherein one or both of the cyclic groups is aromatic and contains one to four heteroatoms selected from O, S, and N. For example, a bicyclic heteroaryl can contain from 8 to 12 ring atoms, and from 1 to 3 heteroatoms selected from O, N, and S in each ring. In one embodiment, one or both cyclic groups is independently optionally substituted with one or more of the following groups: -V-halogen, -(C_1-C_6)-alkyl, -(C_2-C_6)-alkenyl, -(C_2-C_6)-alkynyl, - V-N(R')$_2$, methylenedioxo, ethylenedioxo, -V-NHSO$_2$R', -V-NR'COR', -V-NHCO$_2$R', -V-NO$_2$, -V-SO$_2$N(R')$_2$, -V-SO$_2$R', -V-OR', -V-COR', -V-CO$_2$R', -V-CON(R')$_2$, or –V-CN, wherein each R' is independently hydrogen, unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl; and wherein each V is independently a bond or (C_1-C_6)-alkyl.

[0030] The term "tricyclic heteroaryl" as used herein refers to three fused cyclic groups, wherein two or three of the cyclic groups is aromatic and at least one aromatic group contains 1 to 4 heteroatoms selected from O, S, and N. For example, a tricyclic aryl can contain from 13 to 18 ring atoms, and from 1 to 3 heteroatoms selected from O, N, and S in each ring. In one embodiment, the cyclic groups are independently substituted with one or more of the following groups: -V-halogen, -(C_1-C_6)-alkyl, -(C_2-C_6)-alkenyl, -(C_2-C_6)-alkynyl, - V-N(R')$_2$, methylenedioxo, ethylenedioxo, -V-NHSO$_2$R', -V-NR'COR', -V-NHCO$_2$R', -V-NO$_2$, -V-SO$_2$N(R')$_2$, -V-SO$_2$R', -V-OR', -V-COR', -V-CO$_2$R', -V-CON(R')$_2$, or –V-CN, wherein each R' is independently hydrogen, unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl; and wherein each V is independently a bond or (C_1-C_6)-alkyl.

[0031] An optionally substituted moiety may be substituted with one or more substituents, examples of which are as illustrated herein. In one embodiment, an "optionally substituted" moiety is substituted with one or more of the following: -V-halogen, -(C_1-C_6)-alkyl, -(C_2-C_6)-alkenyl, -(C_2-C_6)-alkynyl, - V-N(R')$_2$, methylenedioxo, ethylenedioxo, -V-NHSO$_2$R', -V-NR'COR', -V-NHCO$_2$R', -V-NO$_2$, -V-SO$_2$N(R')$_2$, -V-SO$_2$R', -V-OR', -V-COR', -V-CO$_2$R', -V-CON(R')$_2$, or –V-CN, wherein each R' is independently hydrogen, unsubstituted (C_1-C_6)-alkyl, or unsubstituted aryl; and wherein each V is independently a bond or (C_1-C_6)-alkyl.

[0032] When such moieties are substituted, for example, they may typically be mono-, di-, tri- or persubstituted. Examples for a halogen substituent include 1-bromo vinyl, 1-fluoro vinyl, 1,2-difluoro vinyl, 2,2-difluorovinyl, 1,2,2-trifluorovinyl, 1,2-dibromo ethane, 1,2 difluoro ethane, 1-fluoro-2-bromo ethane, CF_2F_3, $CF_2CF_2CF_3$, and the like.

[0033] The term halogen includes bromine, chlorine, fluorine, and iodine.

[0034] For the sake of simplicity, connection points ("-") are not depicted. When an atom or compound is described to define a variable, it is understood that it is intended to replace the variable in a manner to satisfy the valency of the atom or compound. For example, if "X*" was C(R*)=C(R*), both carbon atoms form a part of the ring in order to satisfy their respective valences. Likewise, when divalent substituents are presented, it is understood that they are not limited to the order listed, for example, as used in this specification "OCH$_2$" encompasses CH$_2$O and OCH$_2$.

[0035] The term "administer", "administering", or "administration", as used herein refers to either directly administering a compound or pharmaceutically acceptable salt of the compound or a composition to a animal, or administering a prodrug derivative or analog of the compound or pharmaceutically acceptable salt of the compound or composition to the animal, which can form an equivalent amount of active compound within the animal's body.

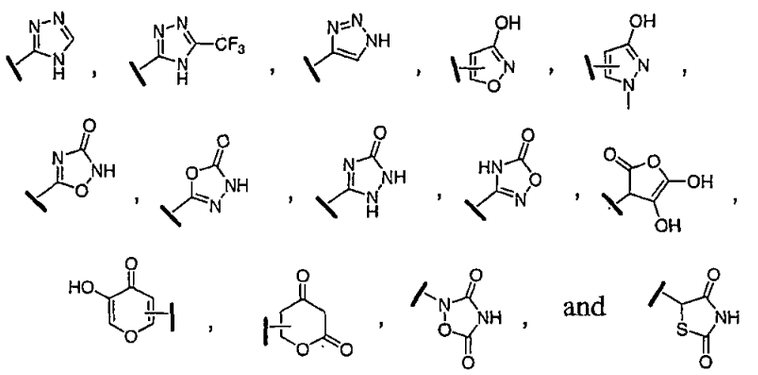
[0036] The term "animal" as used herein includes, without limitation, a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, monkey, chimpanzee, baboon, or rhesus. In one embodiment, the animal is a mammal. In another embodiment, the animal is a human.

[0037] The term "amine protecting group" as used herein refers to a moiety that temporarily blocks an amine reactive site in a compound. Generally, this is done so that a chemical reaction can be carried out at another reactive site in a multifunctional compound or to otherwise stabilize the amine. In one embodiment, an amine protecting group is selectively removable by a chemical reaction. An exemplary amine protecting group is a 9-fluorenylmethoxycarbonyl protecting group. Another exemplary amine protecting group is a carbamate protecting group. Carbamate protecting groups include, without limitation, t-butyl carbamate, methyl carbamate, ethyl carbamate, 2,2,2-trichloroethyl carbamate, 2-(trimethylsilyl)ethyl carbamate, 1,1-dimethyl-2,2,2-trichloroethyl carbamate, benzyl carbamate, p-methoxybenzyl carbamate, p-nitrobenzylcarbamate, p-bromobenzyl carbamate, p-chlorobenzyl carbamate, and 2,4-dichlorobenzyl carbamate. *See*, Greene and Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, John Wiley & Sons (1991).

[0038] The term "carboxylic acid protecting group" as used herein refers to a moiety that temporarily blocks a carboxylic acid reactive site in a compound. Generally, this is done so that a chemical reaction can be carried out at another reactive site in a multifunctional compound or to otherwise stabilize the carboxylic acid. In one embodiment, a carboxylic acid protecting group is selectively removable by a chemical reaction. An exemplary carboxylic acid protecting group is an alkyl ester protecting group, such as a tert-butyl ester.

[0039] The term "acid mimetic group" as used herein refers to a moiety that has chemical and physical similarities producing broadly similar biological properties to an

acid. In one embodiment, an acid mimetic group is a 5 or 6-membered heterocycle containing 1 to 4 heteroatoms selected from O, N, S. Exemplary acid mimetic groups include:



[0040] The term "conditions effective to" as used herein refers to synthetic reaction conditions which will be apparent to those skilled in the art of synthetic organic chemistry.

[0041] The term "effective amount" as used herein refers to an amount of a compound or pharmaceutically acceptable salt of a compound that, when administered to an animal, is effective to prevent, to at least partially ameliorate, or to cure, a condition from which the animal suffers or is suspected to suffer.

[0042] The term "metalloproteinase-related disorder" used herein refers to a condition for which it would be beneficial to modulate activity of the metalloproteinase. Exemplary metalloproteinase-related disorders include, without limitation, arthritic disorders, osteoarthritis, cancer, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, atherosclerosis, age-related macular degeneration, myocardial infarction, corneal ulceration and other ocular surface diseases, hepatitis, aortic aneurysms, tendonitis, central nervous system diseases, abnormal wound healing, angiogenesis, restenosis, cirrhosis, multiple sclerosis, glomerulonephritis, graft versus host disease, diabetes, inflammatory bowel disease, shock, invertebral disc degeneration, stroke, osteopenia, and periodontal diseases.

[0043] The term "metalloproteinase modulator" refers to a compound that is capable of modulating the expression of a metalloproteinase. For example, a metalloproteinase modulator may enhance metalloproteinase expression. A metalloproteinase modulator may also be an inhibitor of a metalloproteinase.

[0044] The term "isolated and purified" as used herein refers to an isolate that is separate from other components of a reaction mixture or a natural source. In certain embodiments, the isolate contains at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 98% of the compound or pharmaceutically acceptable salt of the compound by weight of the isolate.

[0045] As used herein, a compound of the invention includes a pharmaceutically acceptable salt thereof. The term "pharmaceutically acceptable salt" as used herein refers to a salt of an acid and a basic nitrogen atom of a compound of the present invention. Exemplary salts include, but are not limited to, sulfate, citrate, acetate, oxalate, chloride, hydrochloride, bromide, hydrobromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, camphorsulfonate, napthalenesulfonate, propionate, succinate, fumarate, maleate, malonate, mandelate, malate, phthalate, and pamoate. The term "pharmaceutically acceptable salt" as used herein also refers to a salt of a compound of the present invention having an acidic functional group, such as a carboxylic acid functional group, and a base. Exemplary bases include, but are not limited to, hydroxide of alkali metals including sodium, potassium, and lithium; hydroxides of alkaline earth metals such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, organic amines such as unsubstituted or hydroxyl-substituted mono-, di-, or tri-alkylamines, dicyclohexylamine; tributyl amine; pyridine; N-methyl, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-OH-(C_1-C_6)-alkylamine), such as N,N-dimethyl-N-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; morpholine; thiomorpholine; piperidine; pyrrolidine; and amino acids such as arginine, lysine, and the like. The term "pharmaceutically acceptable salt" also includes a hydrate of a compound of the present invention.

[0046] The term "substantially free of its corresponding opposite enantiomer" as used herein means that the compound contains no more than about 10% by weight of its corresponding opposite enantiomer. In other embodiments, the compound that is substantially free of its corresponding opposite enantiomer contains no more than about

5%, no more than about 1%, no more than about 0.5%, or no more than about 0.1% by weight of its corresponding opposite enantiomer. An enantiomer that is substantially free of its corresponding opposite enantiomer includes a compound that has been isolated and purified or has been prepared substantially free of its corresponding opposite enantiomer.

[0047] The term "tautomer" as used herein refers to compounds produced by the phenomenon wherein a proton of one atom of a molecule shifts to another atom. *See*, Jerry March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, Fourth Edition, John Wiley & Sons, pages 69-74 (1992).

[0048] The following abbreviations as used herein mean: Ac is acetate; boc is t-butyl carbamate; Bu is butyl; DIEA is diisopropylethylamine; DMF is dimethylformamide; DMSO is dimethylsulfoxide; ESI is electrospray ionization; Et is ethyl; HPLC is high pressure liquid chromatography; HRMS is high resolution mass spectrometry; Me is methyl; MS is mass spectrometry; *m/z* is mass-to-charge ratio; r.t. is retention time; TFA is trifluoroacetic acid; THF is tetrahydrofuran; FMOC is 9-fluorenylmethoxycarbonyl; DEA is diethylamine; DME is dimethoxyethane; Bop is benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate; PyBop is benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate; HBTU is O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate; and EDC is 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride.

Compounds and Pharmaceutically Acceptable Salts of Compounds of the Invention

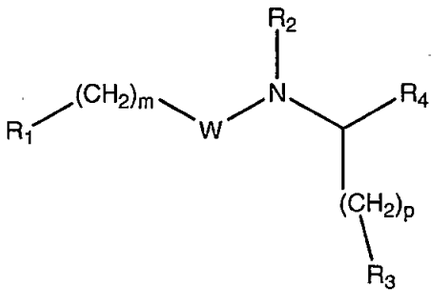
[0049] The compounds or pharmaceutically acceptable salts of compounds of the present invention can contain an asymmetric carbon atom and some of the compounds or pharmaceutically acceptable salts of compounds of the invention can contain one or more asymmetric centers, and can thus give rise to optical isomers and diastereomers. While depicted without respect to stereochemistry in the compounds or pharmaceutically acceptable salts of compounds of the present invention, the present invention includes such optical isomers and diastereomers, as well as racemic and resolved, enantiomerically pure R and S stereoisomers, and also other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof. Where a stereoisomer is provided, it can in some embodiments be provided substantially free of its corresponding opposite enantiomer.

[0050] In addition, the compounds and pharmaceutically acceptable salts of compounds of the present invention can exist as tautomers. Such tautomers can be transient or isolatable as a stable product. These tautomers are within the scope of the present invention.

[0051] Prodrugs of the compounds or pharmaceutically acceptable salts of compounds are also within the scope of the present invention.

Compounds of the Formula (I)

[0052] In one embodiment, the present invention is directed to compounds of the Formula (I):



(I)

and pharmaceutically acceptable salts thereof,

wherein

W is –C(O)-, -OC(O)-, –NHC(O)-, -C(O)O-, or –C(O)NH-;

R_1 is phenyl, heteroaryl, biphenyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each optionally substituted with one or more of R_5 or R_6, and when R_1 is substituted with more than one of R_5 or R_6, the substituents can be identical or different;

R_2 is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -$(CH_2)_nR_{11}$, -OH, or -O-(C_1-C_6) alkyl;

R_3 is -CO_2H, -$CONH_2$, -CONHOH, -$CONHSO_2R_7$, tetrazole, -SO_2NHR_7, -SO_3H, -$PO(OH)NH_2$, -$PO(OH)OR_7$, -$CONHR_7$, -$COOR_7$, an acid mimetic group, or a 5 or 6-membered heterocycloalkyl or heteroaryl containing 1 to 4 heteroatoms selected from O, N, S;

R_4 is -CO_2H, -$CONH_2$, -$(CH_2)_nOR_7$, or -$CONR_9R_{10}$;

R_5 is aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, -CO-(C_1-C_6) alkyl, -CO-aryl, -CO-heteroaryl, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2NH-aryl, -SO_2NH-heteroaryl, -$NHSO_2$-(C_1-C_6) alkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl, -CONH-heteroaryl, (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, or -CONH-(C_3-C_6) cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different;

R_6 and R_{12} are each independently hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6) alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_9 and R_{10} are each independently hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkyl-OH,

(C_1-C_6) alkyl-O-(C_1-C_6) alkyl, aryl, cycloalkyl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_9 and R_{10} together may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_{11} is aryl, heteroaryl, or cycloalkyl;

R_{13} is halogen, -O-(C_1-C_6) alkyl, -CO_2H, -OH, -CF_3, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl substituted with -OH, aryl substituted with -NH_2, aryl substituted with -O-(C_1-C_6) alkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl;

m is 0-4;

n is 0-4; and

p is 0-2.

[0053] In one embodiment, W is -CO.

[0054] In another embodiment, R_3 is -CO_2H.

[0055] In one embodiment, R_1 is bicyclic aryl optionally substituted with one or more of R_5 and R_6.

[0056] In another embodiment, R_1 is tricyclic aryl optionally substituted with one or more of R_5 and R_6.

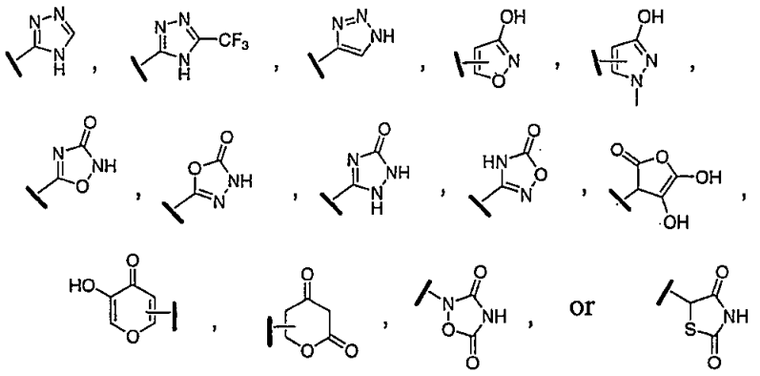
[0057] In one embodiment, R_1 is biphenyl optionally substituted with one or more of R_5 and R_6.

[0058] In one embodiment, m is 0-2. In another embodiment, m is 0.

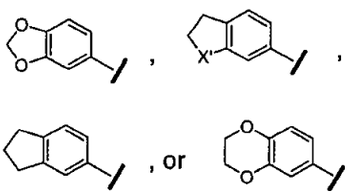
[0059] In one embodiment, p is 0-2. In another embodiment, p is 2.

[0060] In another embodiment, m is 0 and p is 2.

[0061] In another embodiment, R_3 is



[0062] In another embodiment, R_5 is



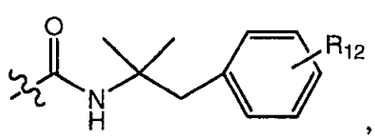
wherein X' is O, S, or NH.

[0063] In one embodiment, R_4 is $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, or $-CONR_9R_{10}$.

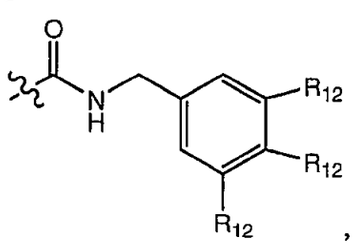
[0064] In one embodiment, W is –CO, R_2 is hydrogen, R_3 is $-CO_2H$, R_1 is biphenyl optionally substituted with one or more of R_5 and R_6, R_4 is $-CONR_9R_{10}$, m is 0, and p is 2.

[0065] In another embodiment, when R_4 is other than hydrogen, the compound or pharmaceutically acceptable salt of the compound is the S-enantiomer with respect to the carbon to which R_4 is bound.

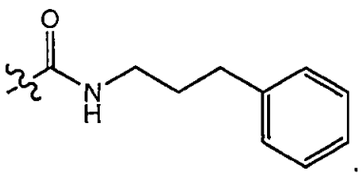
[0066] In one embodiment, R_2 is hydrogen,

R_4 is  , and R_{12} is -F.

[0067] In one embodiment, R_2 is hydrogen,

R_4 is  , and each R_{12} is $-OCH_3$.

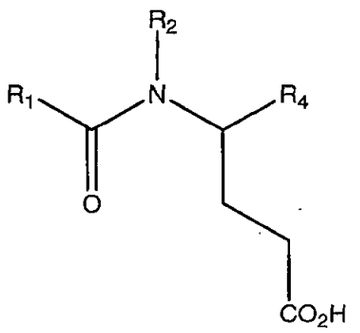
[0068] In another embodiment, R_2 is hydrogen; and



R_4 is .

Compounds of the Formula (Ia)

[0069] In one embodiment, the invention is directed to compounds of the Formula (Ia):



(Ia)

and pharmaceutically acceptable salts thereof,

wherein

R_1 is phenyl, heteroaryl, biphenyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each optionally substituted with one or more of R_5 or R_6, and when R_1 is substituted with more than one of R_5 or R_6, the substituents can be identical or different;

R_2 is hydrogen, $(C_1\text{-}C_6)$ alkyl, $(C_2\text{-}C_6)$ alkenyl, $(C_2\text{-}C_6)$ alkynyl, $-(CH_2)_nR_{11}$, -OH, or $-O\text{-}(C_1\text{-}C_6)$ alkyl;

R_4 is $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, or $-CONR_9R_{10}$;

R_5 is aryl, heteroaryl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, $-CO\text{-}(C_1\text{-}C_6)$ alkyl, -CO-aryl, -CO-heteroaryl, $-SO_2\text{-}(C_1\text{-}C_6)$ alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl, $-SO_2$NH-aryl, $-SO_2$NH-heteroaryl, $-NHSO_2\text{-}(C_1\text{-}C_6)$ alkyl, $-NHSO_2$-aryl, $-NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl, -CONH-heteroaryl, $(C_1\text{-}C_6)$ alkyl, $-O\text{-}(C_1\text{-}C_6)$ alkyl, $-S\text{-}(C_1\text{-}C_6)$ alkyl, $-NH\text{-}(C_1\text{-}C_6)$ alkyl, $-NHCO\text{-}(C_1\text{-}C_6)$ alkyl, $-CONH\text{-}(C_1\text{-}C_6)$ alkyl, $-O\text{-}(C_3\text{-}C_6)$

cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, or -CONH-(C_3-C_6) cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different;

R_6 and R_{12} are each independently hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6) alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_9 and R_{10} are each independently hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkyl-OH, (C_1-C_6) alkyl-O-(C_1-C_6) alkyl, aryl, cycloalkyl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_9 and R_{10} together may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_{11} is aryl, heteroaryl, or cycloalkyl;

R_{13} is halogen, -O-(C_1-C_6) alkyl, -CO_2H, -OH, -CF_3, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl substituted with -OH, aryl substituted with -NH_2, aryl substituted with -O-(C_1-C_6) alkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; and

n is 0-4.

[0070] In one embodiment, R_1 is bicyclic aryl optionally substituted with one or more of R_5 and R_6.

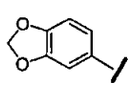
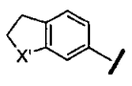
[0071] In another embodiment, R_1 is tricyclic aryl optionally substituted with one or more of R_5 and R_6.

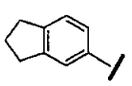
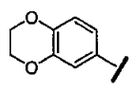
[0072] In one embodiment, R_1 is biphenyl optionally substituted with one or more of R_5 and R_6.

[0073] In one embodiment, R_4 is -CO_2H, -$CONH_2$, -$(CH_2)_nOR_7$, or -$CONR_9R_{10}$.

[0074] In one embodiment, R_1 is biphenyl optionally substituted with one or more of R_5 and R_6, and R_4 is -$CONR_9R_{10}$.

[0075] In another embodiment, R_5 is

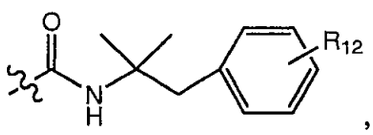

,

,


, or


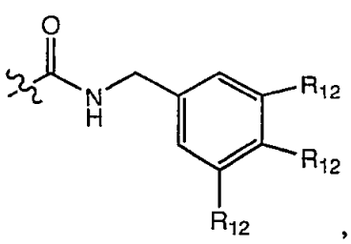
wherein X' is O, S, or NH.

[0076] In another embodiment, when R_4 is other than hydrogen, the compound or pharmaceutically acceptable salt of the compound is the S-enantiomer with respect to the carbon to which R_4 is bound.

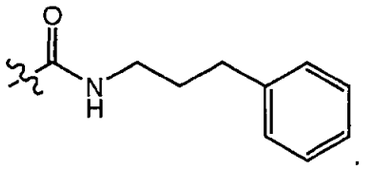
[0077] In one embodiment, R_2 is hydrogen,

R_4 is  , and R_{12} is -F.

[0078] In one embodiment, R_2 is hydrogen,

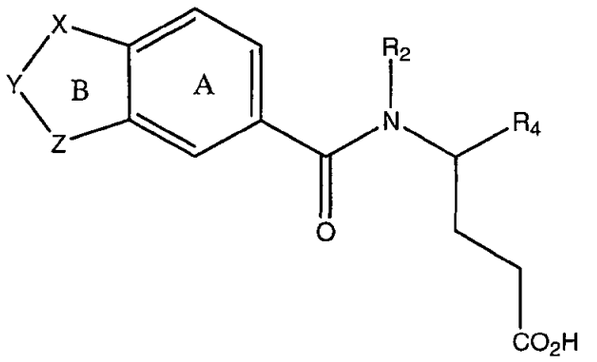
R_4 is  , and each R_{12} is -OCH_3.

[0079] In another embodiment, R_2 is hydrogen; and

R_4 is 

Compounds of the Formula (Ib)

[0080] In one embodiment, the invention is directed to compounds of the Formula (Ib):



(Ib)

and pharmaceutically acceptable salts thereof,

wherein

X, Y, and Z are each independently $(CH_2)_n$, O, S, NR_7, CO, or SO_2; or X, Y, and Z form a benzene in ring B; ring A and ring B are each independently optionally substituted with one or more of R_5 and R_6;

R_2 is hydrogen, $(C_1\text{-}C_6)$ alkyl, $(C_2\text{-}C_6)$ alkenyl, $(C_2\text{-}C_6)$ alkynyl, $-(CH_2)_nR_{11}$, -OH, or $-O\text{-}(C_1\text{-}C_6)$ alkyl;

R_4 is $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, or $-CONR_9R_{10}$;

R_5 is aryl, heteroaryl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, $-CO\text{-}(C_1\text{-}C_6)$ alkyl, -CO-aryl, -CO-heteroaryl, $-SO_2\text{-}(C_1\text{-}C_6)$ alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl, $-SO_2$NH-aryl, $-SO_2$NH-heteroaryl, $-NHSO_2\text{-}(C_1\text{-}C_6)$ alkyl, $-NHSO_2$-aryl, $-NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl,

-CONH-heteroaryl, (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, or -CONH-(C_3-C_6) cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different;

R_6 and R_{12} are each independently hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6) alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_9 and R_{10} are each independently hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkyl-OH, (C_1-C_6) alkyl-O-(C_1-C_6) alkyl, aryl, cycloalkyl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_9 and R_{10} together may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_{11} is aryl, heteroaryl, or cycloalkyl;

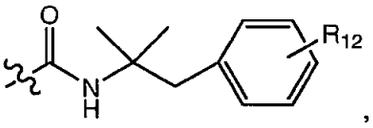
R_{13} is halogen, -O-(C_1-C_6) alkyl, -CO_2H, -OH, -CF_3, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl substituted with -OH, aryl substituted with -NH_2, aryl substituted with -O-(C_1-C_6) alkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; and

n is 0-4.

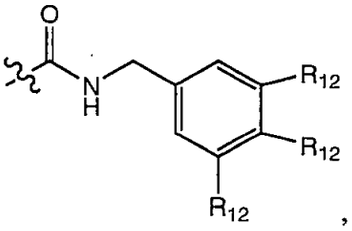
[0081] In one embodiment, R_4 is -CO_2H, -$CONH_2$, -$(CH_2)_nOR_7$, or -$CONR_9R_{10}$.

[0082] In another embodiment, when R_4 is other than hydrogen, the compound or pharmaceutically acceptable salt of the compound is the S-enantiomer with respect to the carbon to which R_4 is bound.

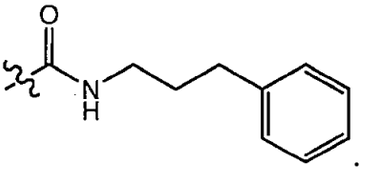
[0083] In one embodiment, R_2 is hydrogen,

R_4 is  , and R_{12} is -F.

[0084] In one embodiment, R_2 is hydrogen;

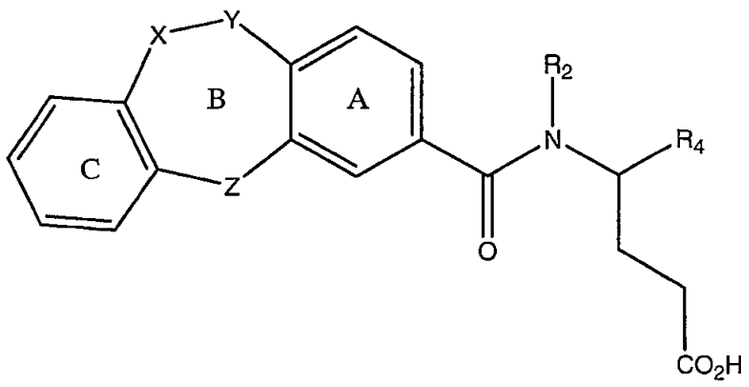
R_4 is  , and each R_{12} is -OCH_3.

[0085] In another embodiment, R_2 is hydrogen; and

R_4 is  .

Compounds of the Formula (Ic)

[0086] In one embodiment, the invention is directed to compounds of the Formula (Ic):



(Ic)

and pharmaceutically acceptable salts thereof,

wherein

X, Y, and Z are each independently $(CH_2)_n$, O, S, NR_7, CO, or SO_2; or X, Y, and Z form a benzene in ring B; ring A, ring B, and ring C are each independently optionally substituted with one or more of R_5 and R_6;

R_2 is hydrogen, $(C_1\text{-}C_6)$ alkyl, $(C_2\text{-}C_6)$ alkenyl, $(C_2\text{-}C_6)$ alkynyl, $-(CH_2)_nR_{11}$, -OH, or $-O\text{-}(C_1\text{-}C_6)$ alkyl;

R_4 is $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, or $-CONR_9R_{10}$;

R_5 is aryl, heteroaryl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, $-CO\text{-}(C_1\text{-}C_6)$ alkyl, -CO-aryl, -CO-heteroaryl, $-SO_2\text{-}(C_1\text{-}C_6)$ alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl, $-SO_2$NH-aryl, $-SO_2$NH-heteroaryl, $-NHSO_2\text{-}(C_1\text{-}C_6)$ alkyl, $-NHSO_2$-aryl, $-NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl, -CONH-heteroaryl, $(C_1\text{-}C_6)$ alkyl, $-O\text{-}(C_1\text{-}C_6)$ alkyl, $-S\text{-}(C_1\text{-}C_6)$ alkyl, $-NH\text{-}(C_1\text{-}C_6)$ alkyl, $-NHCO\text{-}(C_1\text{-}C_6)$ alkyl, $-CONH\text{-}(C_1\text{-}C_6)$ alkyl, $-O\text{-}(C_3\text{-}C_6)$ cycloalkyl, $-S\text{-}(C_3\text{-}C_6)$ cycloalkyl, $-NH\text{-}(C_3\text{-}C_6)$ cycloalkyl, $-NHCO\text{-}(C_3\text{-}C_6)$ cycloalkyl, or $-CONH\text{-}(C_3\text{-}C_6)$ cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different;

R_6 and R_{12} are each independently hydrogen, halogen, -CN, $-OCF_3$, $-CF_3$, $-NO_2$, -OH, -SH, $-NR_7R_8$, $-CONR_7R_8$, $-NR_8COR_7$, $-NR_8CO_2R_7$, $-CO_2R_7$, $-COR_7$, $-SO_2\text{-}(C_1\text{-}C_6)$ alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl, $-SO_2R_7$, $-NR_7SO_2R_8$,

$-SO_2NR_7R_8$; (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6) alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_9 and R_{10} are each independently hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkyl-OH, (C_1-C_6) alkyl-O-(C_1-C_6) alkyl, aryl, cycloalkyl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_9 and R_{10} together may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_{11} is aryl, heteroaryl, or cycloalkyl;

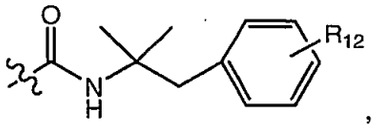
R_{13} is halogen, -O-(C_1-C_6) alkyl, $-CO_2H$, -OH, $-CF_3$, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl substituted with -OH, aryl substituted with $-NH_2$, aryl substituted with -O-(C_1-C_6) alkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; and

n is 0-4.

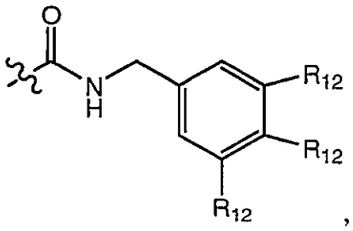
[0087] In one embodiment, R_4 is $-CO_2H$, $-CONH_2$, -$(CH_2)_nOR_7$, or -$CONR_9R_{10}$.

[0088] In another embodiment, when R_4 is other than hydrogen, the compound or pharmaceutically acceptable salt of the compound is the S-enantiomer with respect to the carbon to which R_4 is bound.

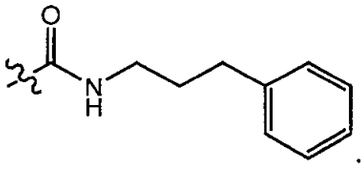
[0089] In one embodiment, R_2 is hydrogen,

R_4 is  , and R_{12} is -F.

[0090] In one embodiment, R_2 is hydrogen;

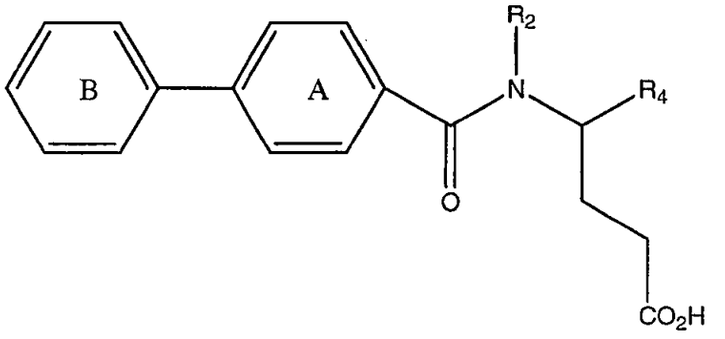
R_4 is  , and each R_{12} is $-OCH_3$.

[0091] In another embodiment, R_2 is hydrogen; and

R_4 is  .

Compounds of the Formula (Id)

[0092] In one embodiment, the invention is directed to compounds of the Formula (Id):



(Id)

and pharmaceutically acceptable salts thereof,

wherein

ring A and ring B are each independently optionally substituted with one or more of R_5 and R_6;

R_2 is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -$(CH_2)_nR_{11}$, -OH, or -O-(C_1-C_6) alkyl;

R_4 is -CO_2H, -$CONH_2$, -$(CH_2)_nOR_7$, or -$CONR_9R_{10}$;

R_5 is aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, -CO-(C_1-C_6) alkyl, -CO-aryl, -CO-heteroaryl, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2NH-aryl, -SO_2NH-heteroaryl, -$NHSO_2$-(C_1-C_6) alkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl, -CONH-heteroaryl, (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, or -CONH-(C_3-C_6) cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different;

R_6 and R_{12} are each independently hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6) alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached

may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_9 and R_{10} are each independently hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkyl-OH, (C_1-C_6) alkyl-O-(C_1-C_6) alkyl, aryl, cycloalkyl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_9 and R_{10} together may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_{11} is aryl, heteroaryl, or cycloalkyl;

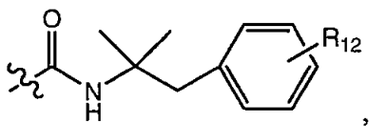
R_{13} is halogen, -O-(C_1-C_6) alkyl, -CO_2H, -OH, -CF_3, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl substituted with -OH, aryl substituted with -NH_2, aryl substituted with -O-(C_1-C_6) alkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; and

n is 0-4.

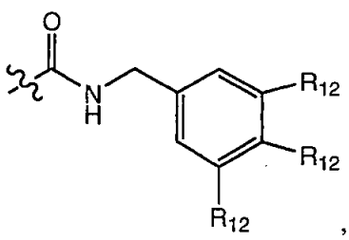
[0093] In one embodiment, R_4 is -CO_2H, -$CONH_2$, -$(CH_2)_nOR_7$, or -$CONR_9R_{10}$.

[0094] In another embodiment, when R_4 is other than hydrogen, the compound or pharmaceutically acceptable salt of the compound is the S-enantiomer with respect to the carbon to which R_4 is bound.

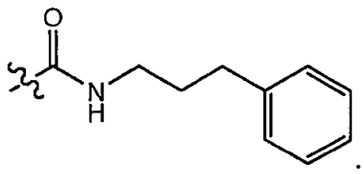
[0095] In one embodiment, R_2 is hydrogen,

R_4 is  , and R_{12} is -F.

[0096] In one embodiment, R_2 is hydrogen;

R_4 is  , and each R_{12} is -OCH_3.

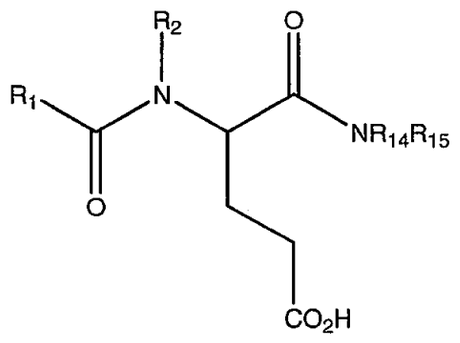
[0097] In another embodiment, R_2 is hydrogen; and



R_4 is .

Compounds of the Formula (II)

[0098] In another embodiment, the invention provides compounds of the Formula (II):



(II)

and pharmaceutically acceptable salts thereof,

wherein

R_1 is phenyl, (C_1-C_6) alkyl substituted with phenyl, heteroaryl, biphenyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each optionally substituted with one or more of R_5 or R_6, and when R_1 is substituted with more than one of R_5 or R_6, the substituents can be identical or different;

R_2 is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -$(CH_2)_pR_{11}$, -OH, or -O-(C_1-C_6) alkyl;

R_5 is aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, -CO-(C_1-C_6) alkyl, -CO-aryl, -CO-heteroaryl, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2NH-aryl, -SO_2NH-heteroaryl, -$NHSO_2$-(C_1-C_6) alkyl, -$NHSO_2$-aryl,

-$NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl, -CONH-heteroaryl, (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, or -CONH-(C_3-C_6) cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different;

R_6 and R_{12} are each independently hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6) alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_{11} is aryl, heteroaryl, or cycloalkyl;

R_{13} is halogen, -O-(C_1-C_6) alkyl, -CO_2H, -OH, -CF_3, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl substituted with -OH, aryl substituted with -NH_2, aryl substituted with -O-(C_1-C_6) alkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl;

R_{14} and R_{15} are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl,

(C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, heterocycloalkyl -$(CH_2)_n$-aryl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_{14} and R_{15} together may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

n is 0-4, and

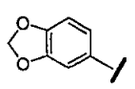
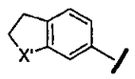
p is 0-2.

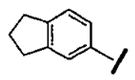
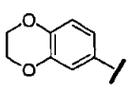
[0099] In one embodiment, R_1 is bicyclic aryl optionally substituted with one or more of R_5 and R_6.

[0100] In another embodiment, R_1 is tricyclic aryl optionally substituted with one or more of R_5 and R_6.

[0101] In one embodiment, R_1 is biphenyl optionally substituted with one or more of R_5 and R_6.

[0102] In another embodiment, R_5 is

 ,  ,

 , or 

wherein X' is O, S, or NH.

[0103] In another embodiment, R_2 is hydrogen.

[0104] In one embodiment, the compound of Formula (I) is N^2-(4-benzoylbenzoyl)-N^1-benzyl-L-α-glutamine, N-(4-benzoylbenzoyl)-L-glutamic acid, N^1-(1,3-benzodioxol-5-ylmethyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-butyl-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclopropyl-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclohexyl-L-α-glutamine, N^1-benzyl-N^2-(4-thien-2-ylbenzoyl)-L-α-glutamine, N^1-benzyl-N^2-[4-(2-furyl)benzoyl]-L-α-glutamine, N^1-benzyl-N^2-[(4'-ethynyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-fluorobenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclooctyl-L-α-glutamine, N^1-benzyl-N^2-(4-bromobenzoyl)-L-α-glutamine, N^1-benzyl-N^2-[(2',5'-dimethyl-1,1'-biphenyl-4-

yl)carbonyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethoxybenzyl)-L-α-glutamine, N^1-benzyl-N^2-(4-pyridin-4-ylbenzoyl)-L-α-glutamine, N^1-benzyl-N^2-[(3',5'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^1-benzyl-N^2-[(4'-ethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^1-benzyl-N^2-[(3'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^1-benzyl-N^2-[(2'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^1-benzyl-N^2-[(2',6'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclopentyl-L-α-glutamine, N^1-[2-(acetylamino)ethyl]-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine, N^1-2-adamantyl-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine, N^1-(2-adamantylmethyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine, N^1-benzyl-N^2-(4-pyridin-2-ylbenzoyl)-L-α-glutamine, N^1-benzyl-N^2-(4-pyridin-3-ylbenzoyl)-L-α-glutamine, N^1-benzyl-N^2-[4-(1,3-thiazol-2-yl)benzoyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methoxybenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3,4-dimethoxyphenyl)ethyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methoxyethyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(4-methoxyphenyl)ethyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(1-naphthylmethyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-methylbenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-furylmethyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-methoxybenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,4-dichlorobenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-(trifluoromethoxy)benzyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[3-(trifluoromethoxy)benzyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-(methylthio)benzyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-phenoxybenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3-methoxyphenyl)ethyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,4-dimethoxybenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methoxybenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dichlorobenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,5-difluorobenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^5-hydroxy-N^1-[3-(trifluoromethoxy)benzyl]-L-glutamamide, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^5-hydroxy-

N^1-[2-(3-methoxyphenyl)ethyl]-L-glutamamide, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^5-hydroxy-N^1-(3,4,5-trimethoxybenzyl)-L-glutamamide, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,5-dimethoxybenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,5-dimethoxybenzyl)-N^5-hydroxy-L-glutamamide, N^1-benzyl-N^2-[(4'-vinyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethylbenzyl)-L-α-glutamine, N^1-benzyl-N^2-[(4'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^1-benzyl-N^2-[(4'-propoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^1-benzyl-N^2-[(4'-butoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^1-benzyl-N^2-{[4'-(cyclobutylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine, N^1-benzyl-N^2-{[4'-(cyclohexylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine, N^2-{[4'-(allyloxy)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethylbenzyl)-N^5-hydroxy-L-glutamamide, N^2-(1,1'-biphenyl-4-ylacetyl)-N^1-(3-methoxybenzyl)-L-α-glutamine, N^2-[(3-fluorophenyl)acetyl]-N^1-(3-methoxybenzyl)-L-α-glutamine, N^2-{[4'-(acetylamino)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutamine, N^1-benzyl-N^2-{[4'-(2-furoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine, N^1-benzyl-N^2-({4'-[(4-fluorobenzoyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutamine, N^2-{[4'-(benzoylamino)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutamine, N^1-benzyl-N^2-(5-phenyl-2-furoyl)-L-α-glutamine, N^1-benzyl-N^2-[5-(3-ethoxyphenyl)-2-furoyl]-L-α-glutamine, N^1-benzyl-N^2-[5-(3,5-dimethylphenyl)-2-furoyl]-L-α-glutamine, N^1-benzyl-N^2-(2,2'-bifuran-5-ylcarbonyl)-L-α-glutamine, N^1-benzyl-N^2-(5-thien-2-yl-2-furoyl)-L-α-glutamine, N^2-[(2,2'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-N^1-(3-methoxybenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-phenylethyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[3-(trifluoromethyl)benzyl]-L-α-glutamine, N^1-(4-aminobenzyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine, N^1-(3-aminobenzyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(trifluoromethyl)benzyl]-L-α-glutamine, N^1-benzyl-N^2-[(2-fluoro-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-fluorobenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine, N^1-benzyl-N^2-(1,1'-biphenyl-3-ylcarbonyl)-L-α-glutamine, N^1-benzyl-N^2-(3-thien-2-ylbenzoyl)-L-α-glutamine, N^1-benzyl-N^2-[(3-chloro-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,

N^1-benzyl-N^2-[(3-fluoro-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^1-benzyl-N^2-[(2,6-dimethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3-chlorophenyl)ethyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-fluorobenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-difluorobenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methylbenzyl)-L-α-glutamine, N^1-benzyl-N^2-({4'-[(3-methoxybenzyl)oxy]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutamine, N^1-benzyl-N^2-({4'-[(3,5-dimethoxybenzyl)oxy]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutamine, N^1-benzyl-N^2-{[4'-(2-naphthylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-2,3-dihydro-1*H*-inden-2-yl-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,3-dimethylbenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-phenylbutyl)-L-α-glutamine, N^1-(2-benzylphenyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methoxy-1,1'-biphenyl-3-yl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methylbenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-fluoro-3-(trifluoromethyl)benzyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-heptyl-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-iodobenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-vinylbenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-thien-2-ylbenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,N^1-benzyl-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine, N^1-(3-methoxybenzyl)-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-*tert*-butylbenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-iodobenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-vinylbenzyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(sec-butyl)-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(cyclopropylmethyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[4-(dimethylamino)benzyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-bromophenyl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-biphenyl-4-ylethyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2'-ethoxybiphenyl-4-yl)ethyl]-L-α-glutamine,N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-ethynylbiphenyl-4-yl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4-(2-thienyl)phenyl]ethyl}-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-pyridin-2-ylphenyl)ethyl]-L-α-

glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[3-(dimethylamino)benzyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(3,3-diphenylpropyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(3,3-dimethylbutyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-isopropyl-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(pyridin-4-ylmethyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1,N^1-diethyl-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1-dimethylpropyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-4-yl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4'-(trifluoromethyl)biphenyl-4-yl]ethyl}-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-3-yl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4'-(trifluoromethyl)biphenyl-3-yl]ethyl}-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-methoxybiphenyl-3-yl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-methoxybiphenyl-4-yl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(3-bromophenyl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-pentyl-L-α-glutamine,N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-pyridin-4-ylphenyl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(*tert*-butyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-{[4'-(trifluoromethyl)biphenyl-3-yl]methyl}-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(2,2-dimethylpropyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[(4'-ethynylbiphenyl-3-yl)methyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(3-pyridin-2-ylbenzyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-hexyl-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(1-methyl-1-phenylethyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1,3,3-tetramethylbutyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-morpholin-4-ylethyl)-L-α-glutamine,N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-hydroxy-1,1-dimethylethyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-fluorophenyl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-chlorophenyl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-thienyl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-chlorophenyl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-(5-hydroxypentyl)-L-α-glutamine, 3-

[(biphenyl-4-ylmethyl)amino]-3-oxopropanoic acid, N^2-(biphenyl-4-ylcarbonyl)-N^1-propyl-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-D-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(3-pyridin-2-ylphenyl)ethyl]-L-α-glutamine, N^2-2-naphthoyl-N^1-(3-phenylpropyl)-L-α-glutamine, N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-[(9-oxo-9*H*-fluoren-2-yl)carbonyl]-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine, N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine, N^2-(4-phenoxybenzoyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-hexyl-L-α-glutamine, N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-hexyl-L-α-glutamine, N^1-hexyl-N^2-(4-phenoxybenzoyl)-L-α-glutamine, N^1-hexyl-N^2-[(9-oxo-9*H*-fluoren-2-yl)carbonyl]-L-α-glutamine, N^2-[(9-oxo-9*H*-fluoren-2-yl)carbonyl]-N^1-(3-phenylpropyl)-L-α-glutamine, N^2-(4-phenoxybenzoyl)-N^1-(3-phenylpropyl)-L-α-glutamine, *N*-[4-(pyrimidin-2-ylamino)benzoyl]-L-glutamic acid, *N*-(1,1'-biphenyl-4-ylcarbonyl)-D-glutamic acid, *N*-[4-(pyrimidin-2-ylamino)benzoyl]-L-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-D-α-glutamine, N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-hydroxybutyl)-L-α-glutamine, N^1-benzyl-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine, N^1-benzyl-N^2-[4-(pyrimidin-2-ylamino)benzoyl]-L-α-glutamine, (4S)-4-[(1,1'-biphenyl-4-ylcarbonyl)amino]-5-hydroxypentanoic acid, *N*-({4'-[(phenylacetyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-glutamic acid, *N*-[(4'-{[(3-methyl-1-benzofuran-2-yl)carbonyl]amino}-1,1'-biphenyl-4-yl)carbonyl]-L-glutamic acid, *N*-{[4'-(2-furoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid, *N*-{[4'-(acetylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid, *N*-{[4'-(benzoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid, *N*-({4'-[(1-benzofuran-2-ylcarbonyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-glutamic acid, N^1-(1,1-dimethyl-2-phenylethyl)-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine, N^1-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine, N^2-(9H-fluoren-2-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine, N^1-(6-hydroxyhexyl)-N^2-(4-phenoxybenzoyl)-L-α-glutamine, N^2-(9H-fluoren-9-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine, N^2-(9H-fluoren-9-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-(3-phenoxybenzoyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-(9H-fluoren-4-

ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^1-1-adamantyl-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine, N^1-1-adamantyl-N^2-(4-phenoxybenzoyl)-L-α-glutamine, N^1-1-adamantyl-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine, N^1-1-adamantyl-N^2-(9H-fluoren-9-ylcarbonyl)-L-α-glutamine, N^2-(9H-fluoren-2-ylcarbonyl)-N^1-(3-methylbenzyl)-L-α-glutamine, N^1-(3-methylbenzyl)-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine, N^2-(9H-fluoren-9-ylcarbonyl)-N^1-(3-methylbenzyl)-L-α-glutamine, N^2-(9H-fluoren-2-ylcarbonyl)-N^1-propyl-L-α-glutamine, N^1-benzyl-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine, N^1-benzyl-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine, N^1-benzyl-N^2-(9H-fluoren-9-ylcarbonyl)-L-α-glutamine, N^1-benzyl-N^2-(3-phenoxybenzoyl)-L-α-glutamine, N^1-(1-methyl-1-phenylethyl)-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine, N^2-(9H-fluoren-9-ylcarbonyl)-N^1-(1-methyl-1-phenylethyl)-L-α-glutamine, N^1-(1-methyl-1-phenylethyl)-N^2-(3-phenoxybenzoyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[(1S)-1-phenylethyl]-L-α-glutamine, N^2-(9H-fluoren-2-ylcarbonyl)-N^1-[(1S)-1-phenylethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[(1S)-1-(4-fluorophenyl)ethyl]-L-α-glutamine, tert-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(1-phenylethyl)-L-α-glutaminate, N^2-(biphenyl-4-ylcarbonyl)-N^1-[(1R)-1-(4-fluorophenyl)ethyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[(1R)-1-phenylethyl]-L-α-glutamine, N^2-(9H-fluoren-2-ylcarbonyl)-N^1-[(1R)-1-phenylethyl]-L-α-glutamine, N^2-(9H-fluoren-1-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine, N^1-(6-hydroxyhexyl)-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-9H-fluoren-9-yl-L-α-glutamine, N^2-(9H-fluoren-2-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-[(3'-ethoxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-[(2'-ethoxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-[(4'-methoxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-(4-bromobenzoyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-[(3'-methoxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, 4'-{[((1S)-3-carboxy-1-{[(3,4,5-trimethoxybenzyl)amino]carbonyl}propyl)amino] carbonyl}biphenyl-3-carboxylic acid, N^2-[(4'-ethylbiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, *N*-benzyl-N^2-[4-(2-naphthyl)benzoyl]-L-α-glutamine, N^2-[(3',4'-dimethoxybiphenyl-4-

yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-[(2',4'-dimethoxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, *N*-(3,4,5-trimethoxybenzyl)-N^2-[(3',4',5'-trimethoxybiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-(1-adamantylmethyl)-N^2-(biphenyl-4-ylcarbonyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(3'-methoxybiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-[(3',4'-dimethoxybiphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(2'-ethoxybiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(3'-fluoro-4'-methylbiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-(4-bromobenzoyl)-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, *N*-[(1S)-1-benzyl-2-hydroxyethyl]-N^2-(biphenyl-4-ylcarbonyl)-L-α-glutamine, *N*-[(1S)-1-benzyl-2-hydroxyethyl]-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine, *N*-(1-adamantylmethyl)-N^2-(4-bromobenzoyl)-L-α-glutamine, *N*-(1-adamantylmethyl)-N^2-[(4'-hydroxybiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-[4-(1,3-benzodioxol-5-yl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, N^2-[(2',4'-dimethoxybiphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, N^2-[(3'-fluoro-4'-methylbiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, *N*-(1-adamantylmethyl)-N^2-({4'-[(3-methoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutamine, *N*-(1-adamantylmethyl)-N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-*N*-methyl-*N*-(2-phenylethyl)-L-α-glutamine, N^2-[(4'-sec-butylbiphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-isopropylbiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-(1,1':4',1"-terphenyl-4-ylcarbonyl)-L-α-glutamine, N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, N^2-[(4'-hydroxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, *N*-(1-adamantylmethyl)-N^2-({3'-[(dimethylamino)carbonyl]biphenyl-4-yl}carbonyl)-L-α-glutamine, *N*-(1-adamantylmethyl)-N^2-[(3',5'-dimethylbiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-(9H-fluoren-2-ylcarbonyl)-*N*-methyl-*N*-(2-phenylethyl)-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(3'-methylbiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-({4'-[(3,5-dimethylbenzyl)oxy]biphenyl-4-yl}carbonyl)-

N-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-[(4'-{[3,5-bis(trifluoromethyl)benzyl]oxy}biphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-[(3'-isopropylbiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-[(4'-isopropylbiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, *N*-(1-adamantylmethyl)-N^2-[4-(1-benzofuran-5-yl)benzoyl]-L-α-glutamine, *N*-(1-adamantylmethyl)-N^2-[4-(1H-indol-5-yl)benzoyl]-L-α-glutamine, N^2-[(3'-ethoxybiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(3'-methoxybiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(3'-isopropylbiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-[(3'-fluoro-4'-methylbiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(4'-isobutylbiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-(1,1':4',1''-terphenyl-4-ylcarbonyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, *N*-benzyl-N^2-{[3'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-L-α-glutamine, *N*-benzyl-N^2-({4'-[(3-fluorobenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutamine, *N*-benzyl-N^2-{[4'-(benzyloxy)biphenyl-4-yl]carbonyl}-L-α-glutamine, *N*-benzyl-N^2-[4-(phenylethynyl)benzoyl]-L-α-glutamine, *N*-benzyl-N^2-{4-[(9-hydroxy-9H-fluoren-9-yl)ethynyl]benzoyl}-L-α-glutamine, *N*-benzyl-N^2-{4-[(1E)-3-oxo-3-phenylprop-1-en-1-yl]benzoyl}-L-α-glutamine, *N*-(3,4,5-trimethoxybenzyl)-N^2-[(2',4',6'-trimethylbiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-({4'-[(3-methoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-hydroxybiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(3'-ethoxybiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(6-hydroxyhexyl)-L-α-glutamine, N^2-({4'-[(3-methoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-(4-bromobenzoyl)-*N*-(3-methylbenzyl)-L-α-glutamine, N^2-[4-(1,3-benzodioxol-5-yl)benzoyl]-*N*-(3-methylbenzyl)-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-*N*-butyl-*N*-methyl-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(4'-hydroxybiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-butyl-N^2-(9H-fluoren-2-ylcarbonyl)-*N*-methyl-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methyl-L-α-glutamine, N^2-[4-(1,3-benzodioxol-5-yl)benzoyl]-

N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(3,4-dimethoxyphenyl)ethyl]-N^2-(9H-fluoren-2-ylcarbonyl)-*N*-methyl-L-α-glutamine, N^2-(9H-fluoren-2-ylcarbonyl)-*N*-[(2R)-2-phenylpropyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-*N*-[(2R)-2-phenylpropyl]-L-α-glutamine, *N*-benzyl-N^2-{4-[(4-hydroxycyclohexyl)ethynyl]benzoyl}-L-α-glutamine, N^2-{4-[(3-aminophenyl)ethynyl]benzoyl}-*N*-benzyl-L-α-glutamine, *N*-benzyl-N^2-[4-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)benzoyl]-L-α-glutamine, *N*-benzyl-N^2-{4-[(3-methoxyphenyl)ethynyl]benzoyl}-L-α-glutamine, N^2-[(3'-hydroxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-{[4'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-methylbiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-glutamamide, N^2-({4'-[(3-tert-butylphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(1,1-dimethyl-2- phenylethyl)-L-α-glutamine, N^2-({4'-[(3,5-di-tert-butylphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(1,1-dimethyl-2 -phenylethyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-({4'-[(3-ethylphenoxy)methyl]biphenyl-4-yl}carbonyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-({4'-[(3-methoxyphenoxy)methyl]biphenyl-4-yl}carbonyl)-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(3'-hydroxybiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-(biphenyl-4ylcarbonyl)-N^1-[2-(4-fluoropenyl)-1,2-dimethylethyl]-N^5-hydroxy-L-glutamanide, N^2-[4-(5-bromo-2-thienyl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(5-chloro-2-thienyl)-1,1-dimethylethyl]-N^2-[(3'-fluorobiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-[(3',4'-difluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(3',4'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(2',4'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(2',5'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(2',6'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(3',5'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(2',3'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-(4-

pyrimidin-5-ylbenzoyl)-L-α-glutamine, N^2-[(3',4'-difluorobiphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, N^2-[(3',5'-difluorobiphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, *N*-[2-(5-chloro-2-thienyl)-1,1-dimethylethyl]-N^2-[(3',4'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-(biphenyl-4-ylcarbonyl)-*N*-[2-(5-chloro-2-thienyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-{[5-(3-chloro-4-fluorophenyl)-2-thienyl]carbonyl}-*N*-[2-(5-chloro-2-thienyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-{[4'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-{[4'-(bromomethyl)biphenyl-4-yl]carbonyl}-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[4-(2-thienyl)benzoyl]-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[4-(2-furyl)benzoyl]-L-α-glutamine, N^2-{[4'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-*N*-(3-methylbenzyl)-L-α-glutamine, N^2-{[3'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-*N*-(3-methylbenzyl)-L-α-glutamine, N^2-[4-(2,3-dihydro-1-benzofuran-5-yl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-[(3'-chloro-4'-fluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-{[3'-(bromomethyl)biphenyl-4-yl]carbonyl}-*N*-(3-methylbenzyl)-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[4-(3-thienyl)benzoyl]-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[4-(5-methyl-2-thienyl)benzoyl]-L-α-glutamine, N^2-[4-(5-chloro-2-thienyl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(2-thienyl)benzoyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-{[5-(3-methoxyphenyl)-2-thienyl]carbonyl}-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(5-phenyl-2-thienyl)carbonyl]-L-α-glutamine, N^2-(2,2'-bithien-5-ylcarbonyl)-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-[4-(2,3-dihydro-1-benzofuran-6-yl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-{[6-(3-methoxyphenyl)pyridin-3-yl]carbonyl}-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(5-phenyl-2-thienyl)carbonyl]-L-α-glutamine, N^2-[(3-fluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(5-pyridin-4-yl-2-thienyl)carbonyl]-L-α-glutamine, N^2-{[5-(3-chloro-

4-fluorophenyl)-2-thienyl]carbonyl}-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(2,3-dihydro-1-benzofuran-6-yl)benzoyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(5-pyridin-3-yl-2-thienyl)carbonyl]-L-α-glutamine, N^2-[4-(2,3-dihydro-1-benzofuran-6-yl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, N^2-{[5-(3-chloro-4-fluorophenyl)-2-thienyl]carbonyl}-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[4-(2-thienyl)benzoyl]-L-α-glutamine,*N*-(1,1-dimethyl-2-phenylethyl)-N^2-{[5-(3-methoxyphenyl)-2-thienyl]carbonyl}-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(5-phenyl-2-thienyl)carbonyl]-L-α-glutamine, N^2-(2,2'-bithien-5-ylcarbonyl)-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(5-pyridin-4-yl-2-thienyl)carbonyl]-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(5-pyridin-3-yl-2-thienyl)carbonyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(5-chloro-2-thienyl)benzoyl]-L-α-glutamine, N^2-{[6-(5-chloro-2-thienyl)pyridin-3-yl]carbonyl}-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-(5-phenyl-2-furoyl)-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-{[6-(5-chloro-2-thienyl)pyridin-3-yl]carbonyl}-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-{[5-(3-methoxyphenyl)-2-thienyl]carbonyl}-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(5-pyridin-3-yl-2-thienyl)carbonyl]-L-α-glutamine, N^2-{[5-(3-chloro-4-fluorophenyl)-2-thienyl]carbonyl}-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-(2,2'-bithien-5-ylcarbonyl)-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(5-formyl-2-thienyl)benzoyl]-L-α-glutamine, N^2-[4-(5-acetyl-2-thienyl)benzoyl]-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(1,3-thiazol-2-yl)benzoyl]-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[4-(1,3-thiazol-2-yl)benzoyl]-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-(5-phenyl-2-furoyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[4-(5-formyl-2-thienyl)benzoyl]-L-α-glutamine, N^2-[4-(5-acetyl-2-thienyl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-

N^2-[3-(5-chloro-2-thienyl)benzoyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[3-(2-thienyl)benzoyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-{[5-(4-chlorophenyl)-2-thienyl]carbonyl}-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-{[5-(4-fluorophenyl)-2-thienyl]carbonyl}-L-α-glutamine, N^2-[4-(5-bromo-2-thienyl)benzoyl]-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-[4-(5-bromo-2-thienyl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-{[5-(4-fluorophenyl)-2-thienyl]carbonyl}-L-α-glutamine, N^2-[3-(5-chloro-2-thienyl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[3-(2-thienyl)benzoyl]-L-α-glutamine, N^2-[(3'-chlorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-[(4'-chlorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-[(4'-fluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-[(3'-fluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(3-phenyl-2-thienyl)carbonyl]-L-α-glutamine, N^2-[(4'-chlorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-[(3'-chlorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-{[5-(4-fluorophenyl)-2-thienyl]carbonyl}-L-α-glutamine, N^2-{[5-(4-chlorophenyl)-2-thienyl]carbonyl}-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(3-phenyl-2-thienyl)carbonyl]-L-α-glutamine, N^2-(4-bromobenzoyl)-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-fluorobiphenyl-4-yl)carbonyl]-L-α-glutamine, *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(3'-fluorobiphenyl-4-yl)carbonyl]-L-α-glutamine, N^2-[4-(5-chloro-2-thienyl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-D-α-glutamine, N^2-{[6-(5-chloro-2-thienyl)pyridin-3-yl]carbonyl}-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-{[5-(4-chlorophenyl)-2-thienyl]carbonyl}-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-{[5-(3,4-difluorophenyl)-2-thienyl]carbonyl}-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, N^2-[(4'-{[3,5-bis(trifluoromethyl)phenoxy]methyl}biphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, N^2-({4'-[(1,3-benzodioxol-5-yloxy)methyl]biphenyl-4-

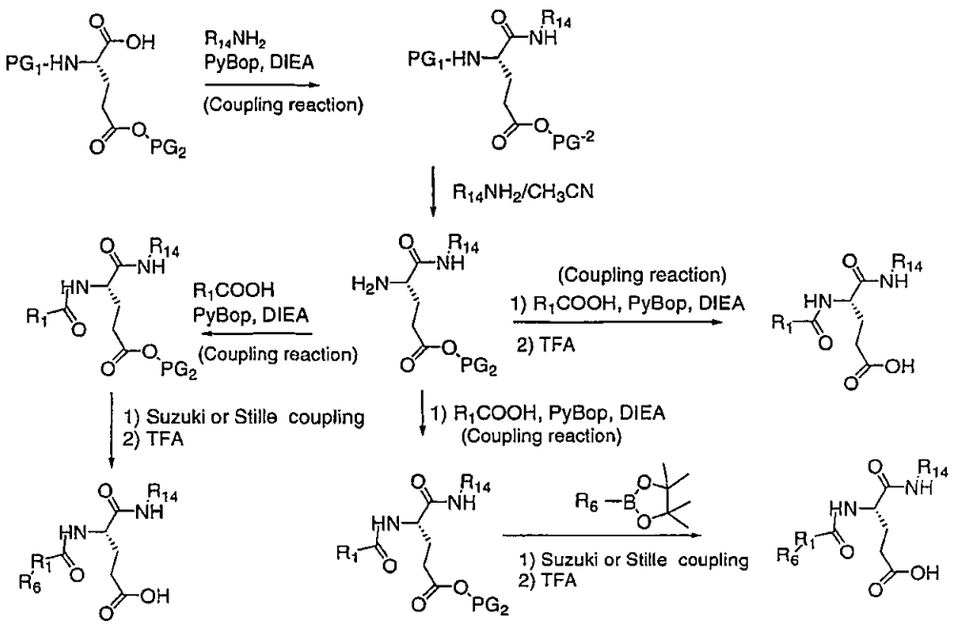
yl}carbonyl)-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine, N^2-{[3'-(benzyloxy)biphenyl-4-yl]carbonyl}-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-({3'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-({3'-[(3-methoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine, *N*-benzyl-N^2-{[4'-(biphenyl-3-ylmethoxy)biphenyl-4-yl]carbonyl}-L-α-glutamine, *N*-benzyl-N^2-({4'-[(3'-methoxybiphenyl-3-yl)methoxy]biphenyl-4-yl}carbonyl)-L-α-glutamine, N^2-({4'-[(3,5-dimethoxyphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(3-methylbenzyl)-L-α-glutamine, N^2-({3'-[(3,5-dimethoxyphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(3-methylbenzyl)-L-α-glutamine, N^2-[(3'-{[3,5-bis(trifluoromethyl)phenoxy]methyl}biphenyl-4-yl)carbonyl]-*N*-(3-methylbenzyl)-L-α-glutamine, N^2-({3'-[(3-ethylphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(3-methylbenzyl)-L-α-glutamine, *N*-benzyl-N^2-{[4'-(biphenyl-2-ylmethoxy)biphenyl-4-yl]carbonyl}-L-α-glutamine, or *N*-benzyl-N^2-({4'-[(3'-methoxybiphenyl-2-yl)methoxy]biphenyl-4-yl}carbonyl)-L-α-glutamine.

Methods for Making the Compounds and Pharmaceutically Acceptable Salts of Compounds of the Invention

[0105] The compounds and pharmaceutically acceptable salts of compounds of the present invention can be prepared using a variety of methods starting from commercially available compounds, known compounds, or compounds prepared by known methods. General synthetic routes to many of the compounds of the invention are included in the following schemes. It is understood by those skilled in the art that protection and deprotection steps not shown in the Schemes may be required for these syntheses, and that the order of steps may be changed to accommodate functionality in the target molecule.

[0106] As used in the schemes, PG_1 is an amine protecting group; PG_2 is a carboxylic acid protecting group; and R_1, R_2, R_6, R_{12}, R_{13}, R_{14}, and R_{15} are defined as above.

General synthetic schemes for preparation of compounds



[0107] The amide formation between a carboxylic acid and an amine is carried out using a coupling reagent in a solvent such as DMF. Coupling reagents that may be used include benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (Bop reagent), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBop reagent), O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate (HBTU), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC), and other known or commercially available coupling reagents.

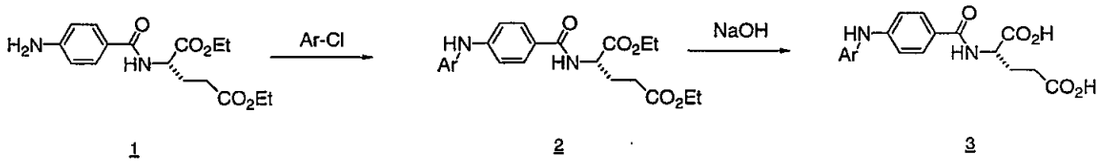
[0108] Cross coupling is generally referred to as Suzuki or Stille coupling reactions.

[0109] The amine protecting group is cleaved under mild conditions with an amine base to afford the free amine. A variety of amine bases may be used, including for example, diethylamine, piperidine, morpholine, dicyclohexylamine, p-dimethylaminopyridine, or diisopropylethylamine in a solvent, such as acetonitrile or DMF.

[0110] Hydrolysis of the carboxylic acid protecting group is carried out using TFA, NaOH, LiOH, potassium carbonate, or the like.

[0111] Scheme 1 demonstrates the preparation of compounds of the invention in two steps from N-(4-aminobenzoyl)-L-glutamic diethyl ester (1). Heating an aryl or heteroaryl chloride such as chloropyridine with N-(4-aminobenzoyl)-L-glutamic diethyl ester gave the diethyl ester (2), which was hydrolyzed with bases such as NaOH, LiOH, or the like to provide (3).

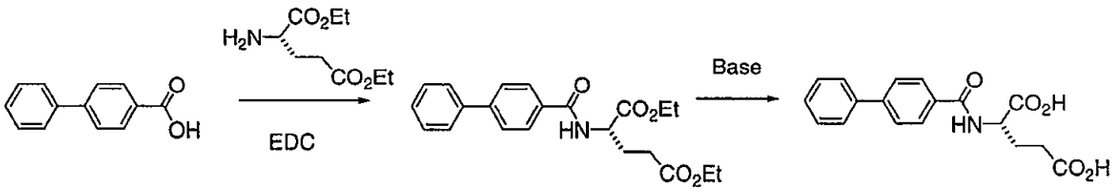
Scheme 1



1 2 3

[0112] Scheme 2 provides the preparation of a compound of the invention in two steps from biphenylcarboxylic acid (4). Amide formation was carried out using a coupling reagent, such as EDC. Hydrolysis of the diethyl ester (5) under basic conditions gave the final product dicarboxylic acid (6).

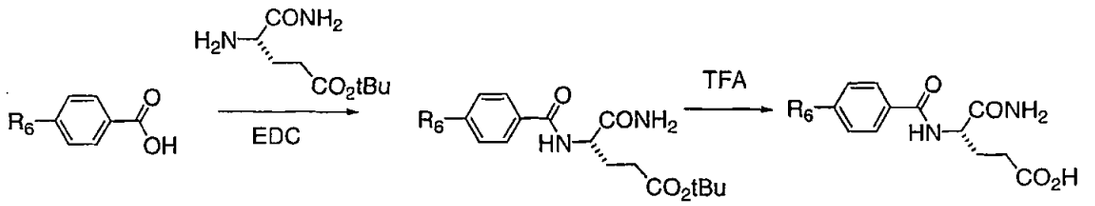
Scheme 2



4 5 6

[0113] Scheme 3 provides the preparation of compounds of the invention in two steps. Coupling of the amine and carboxylic acid (7) was carried out using a coupling reagent such as EDC. The tert-butyl protecting group on (8) was hydrolyzed in acidic conditions (TFA in dichloromethane) to provide the product (9).

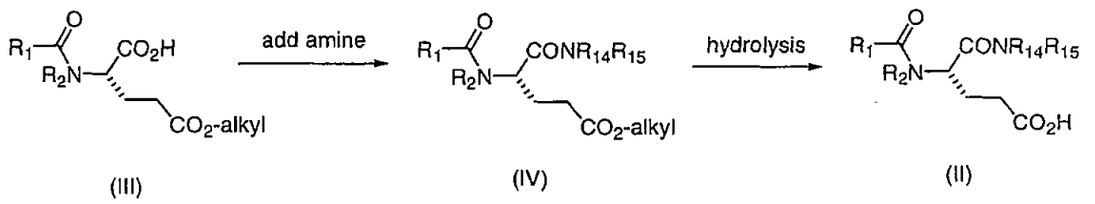
Scheme 3



7 8 9

[0114] Scheme 4 demonstrates the synthesis of a compound or pharmaceutically acceptable salt of a compound of the Formula (II). As shown in Scheme 4, a compound of the Formula (III) is treated with an amine under conditions effective to provide a compound of the Formula (IV). Hydrolysis of the alkyl ester provides a compound of the Formula (II).

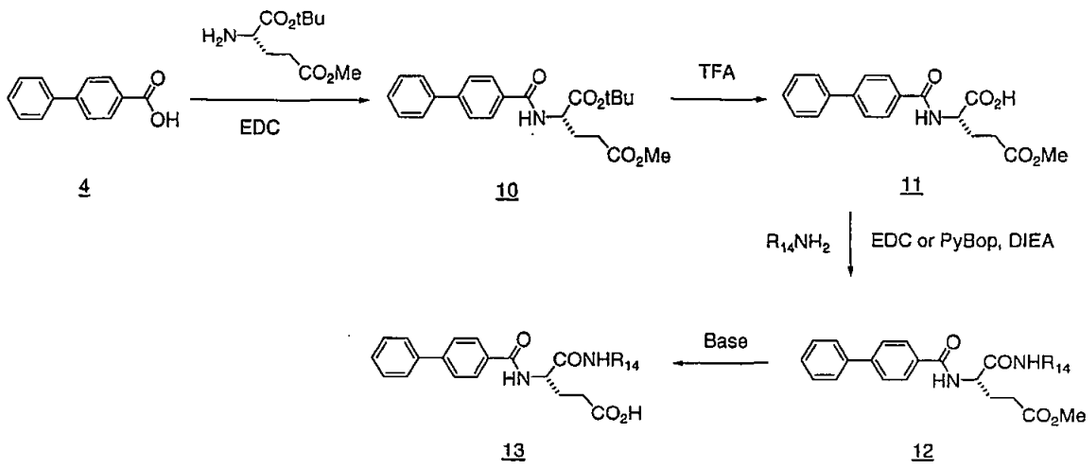
Scheme 4



(III) (IV) (II)

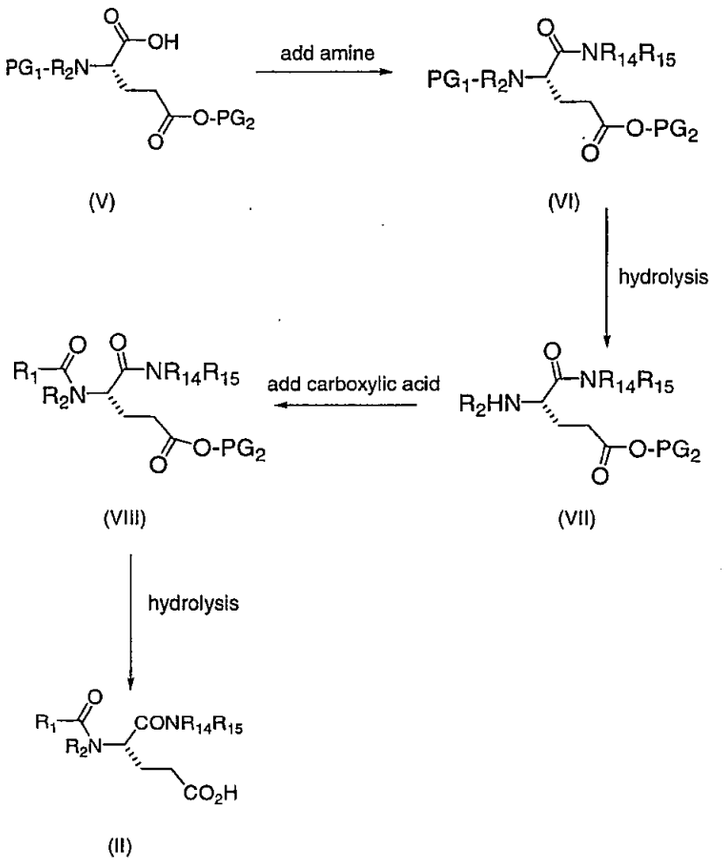
[0115] Scheme 5 provides the synthesis of compounds of the Formula (II) following the general procedures set forth in Scheme 4. Coupling of commercially available amines, amines known in the literature, or other amines with biphenylcarboxylic acid (**4**, or fluorencarboxylic acids or other carboxylic acids) can be carried out in EDC, PyBop/DIEA, or other coupling reagents as described above in the general scheme. Hydrolysis of the tert-butyl ester (**10**) was carried out using TFA. The second coupling reaction of the carboxylic acid (**11**) with a variety of amines was carried out using a similar procedure as employed in the first step. Finally, the methyl ester (**12**) was hydrolyzed with NaOH/MeOH in THF to provide (**13**).

Scheme 5



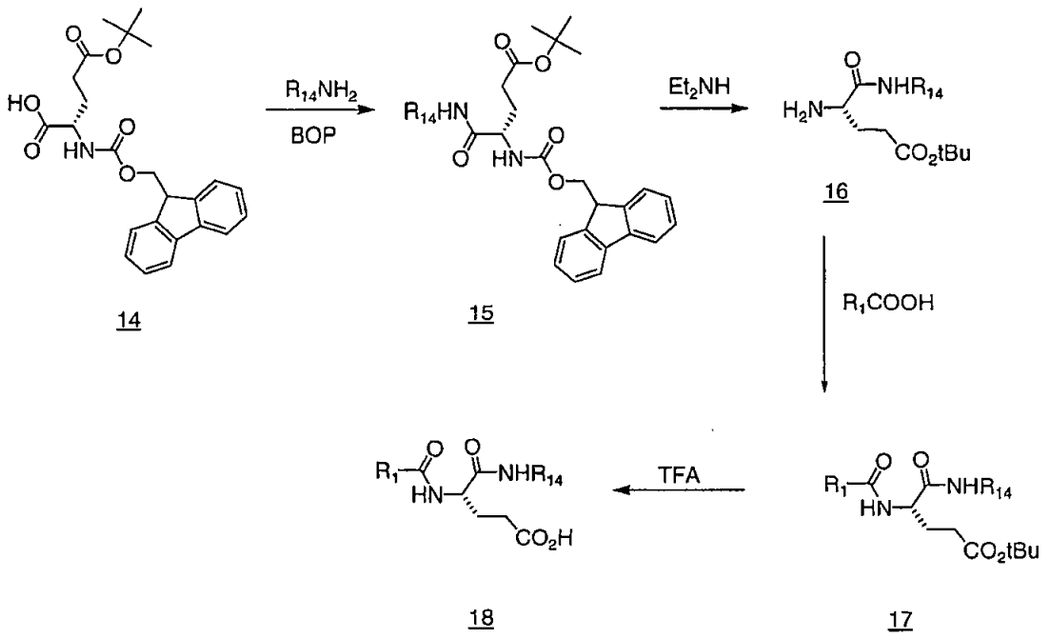
[0116] Scheme 6 demonstrates the synthesis of a compound or pharmaceutically acceptable salt of a compound of the Formula (II). As shown in Scheme 6, a compound of the Formula (V) is treated with an amine under conditions effective to provide a compound of the Formula (VI). Hydrolysis of the amine protecting group provides a compound of the Formula (VII), which is coupled with a carboxylic acid under conditions effective to provide a compound of the Formula (VIII). Hydrolysis of the protected carboxylic acid provides a compound of the Formula (II).

Scheme 6



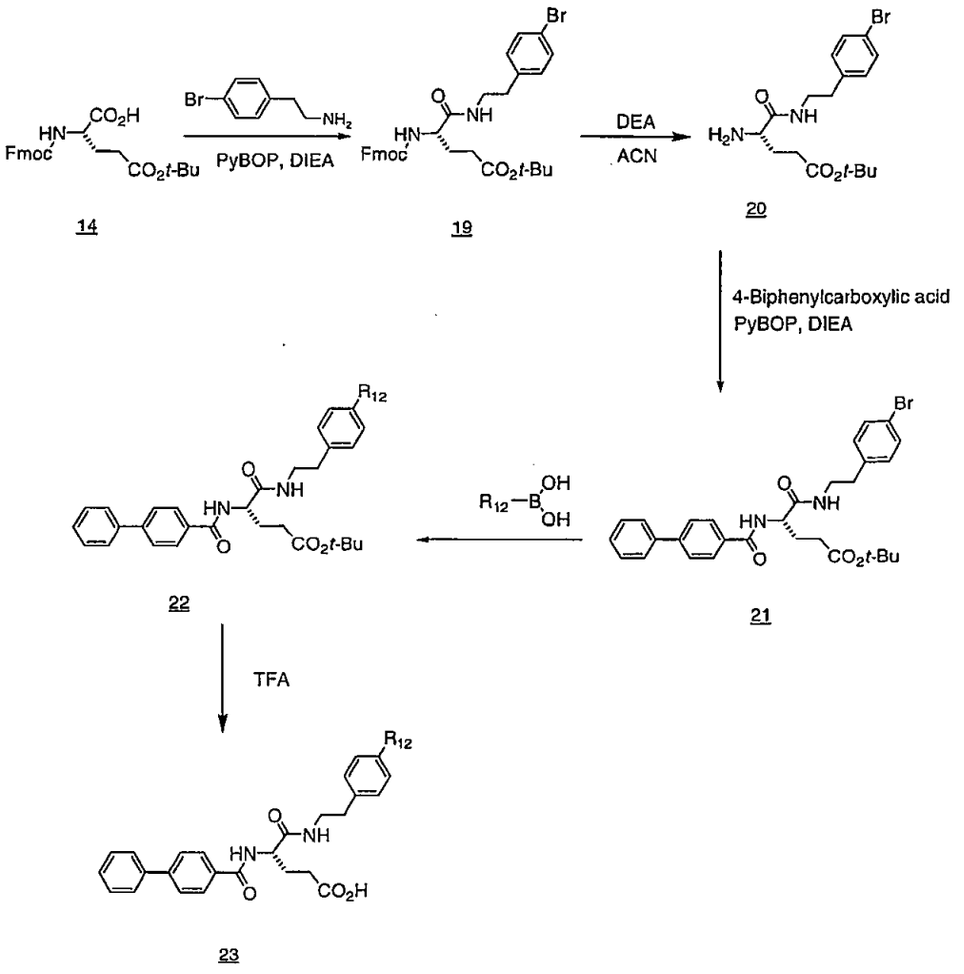
[0117] Scheme 7 provides the synthesis of compounds of the Formula (II) following the general procedures set forth in Scheme 6. In scheme 7, Fmoc-glu(Obut)OH (**14**) was reacted with a known or or commercially available primary or secondary amine. Hydrolysis of the Fmoc protecting group of (**15**) was carried out with diethylamine in acetonitrile. The amine (**16**) was then coupled with a carboxylic acid (e.g. 4-biphenylcarboxylic acid or fluorencarboxylic acid) and the resulting tert-butyl ester (**17**) was hydrolyzed using TFA in dichloromethane to provide (**18**).

Scheme 7



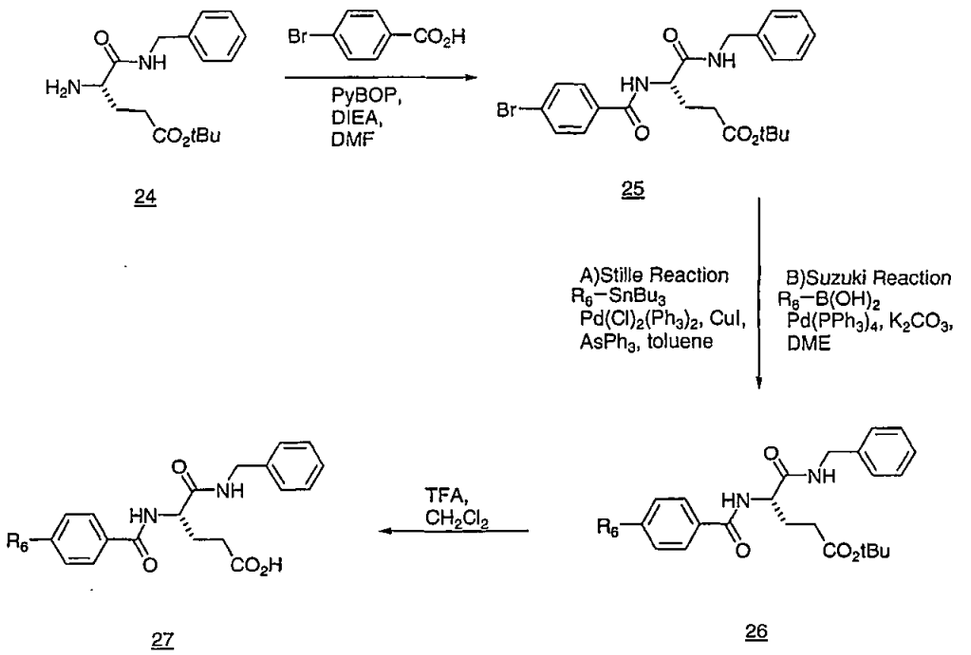
[0118] Scheme 8 demonstrates the preparation of compounds of the invention similar to the procedure described in scheme 7. Bromo or iodophenethylamine (or bromo or iodo benzylamine) was coupled with the Fmoc protected amino acid (**14**). Removal of the Fmoc protecting group of (**19**) was carried out in base and the resulting compound (**20**) was reacted with 4-biphenylcarboxylic acid (or fluorencarboxylic acid or other carboxylic acid). Cross-coupling of the bromo or iodo intermediate (**21**) with a boronic ester or stannyl reagent (via Suzuki or Stille method) gave the coupling product t-butyl ester (**22**), which was then hydrolyzed to give the final carboxylic acid product (**23**).

Scheme 8



[0119] Scheme 9 demonstrates the preparation of compounds of the invention in three steps from bromo compounds. Cross coupling of (**25**) with either a boronic ester or a stannyl compound using either Suzuki or Stille coupling gave the tert-butyl ester (**26**), which was then hydrolyzed to the carboxylic acid (**27**).

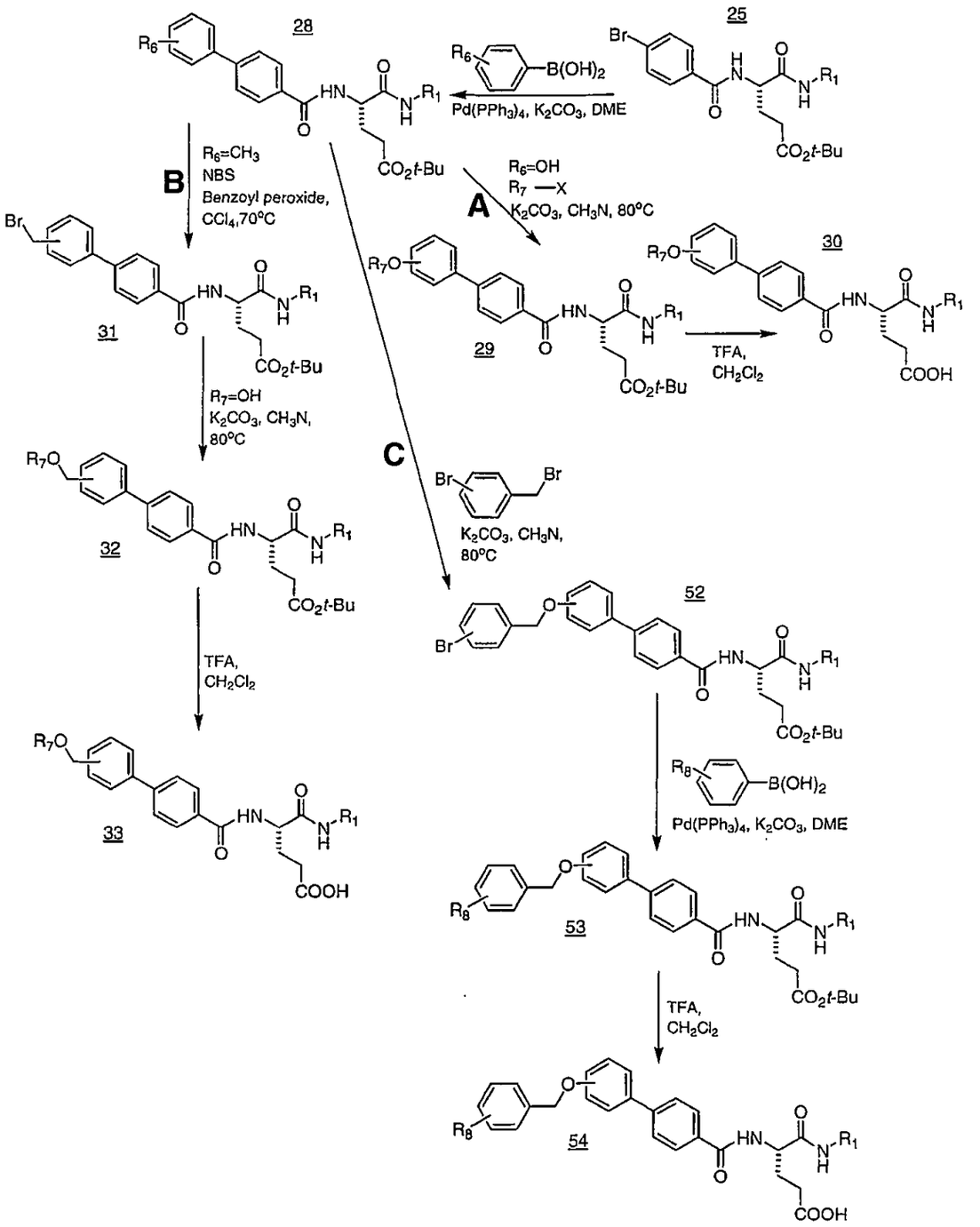
Scheme 9



24 25 26 27

[0120] Scheme 10 provides compounds of the invention prepared in three or four steps from bromo compounds. Suzuki coupling of (**25**) with the 4-hydroxyphenylboronic acid gave the intermediate (**28**). Path A: Alkylation of the phenolic compound with an alkylhalide or benzyl halide provided (**29**), followed by acid hydrolysis to give the carboxylic acid (**30**). Path B: The brominated compound (**31**) was treated with an alcohol to give (**32**), followed by acid hydrolysis to give the carboxylic acid (**33**). Path C: The intermediate (**28**) was treated a bromobenzylbromide compound to provide (**52**), followed by treatment with phenylboronic acid to provide (**53**), which was then acid hydrolized to give (**54**).

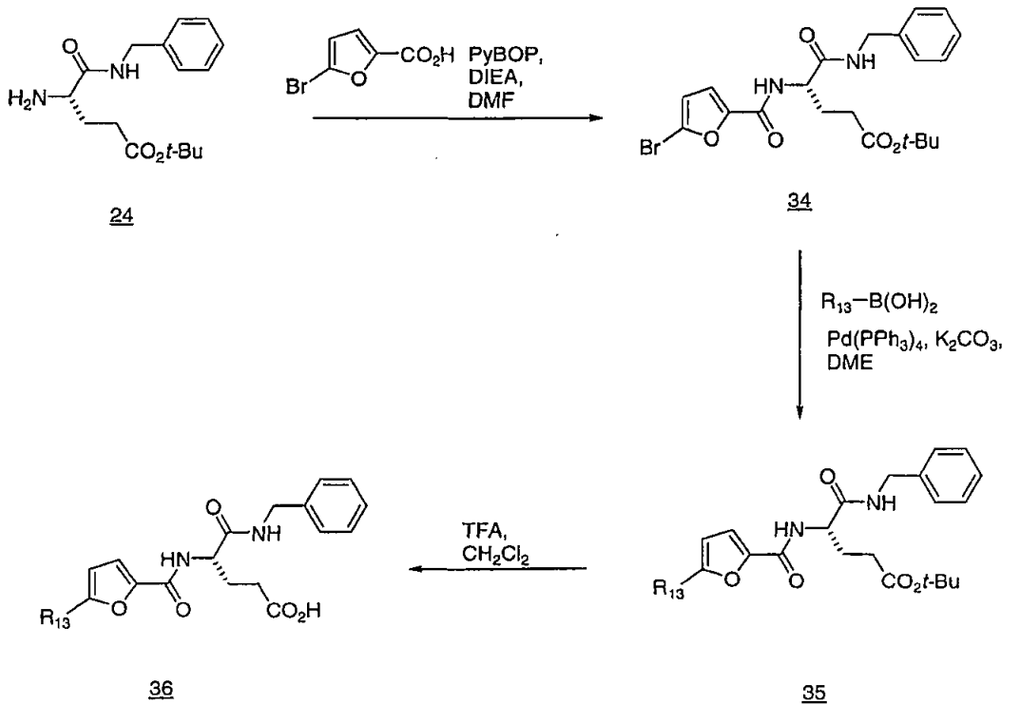
Scheme 10



[0121] Scheme 11 provides compounds of the invention prepared in a similar manner described in scheme 10, except 5-bromofuroic acid was used in the first coupling

reaction step. The bromo intermediate (34) was then reacted with a boronic acid and hydrolysis of the resulting tert-butyl ester (35) in acid provided the carboxylic acid (36).

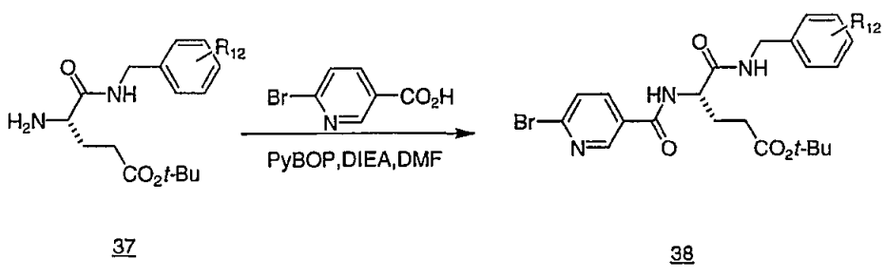
Scheme 11



24 34 36 35

[0122] Scheme 12 provides compounds of the invention prepared according to the procedure described in scheme 11, except 6-bromonicotinic acid was used to couple with the amino intermediate (37) to afford (38).

Scheme 12

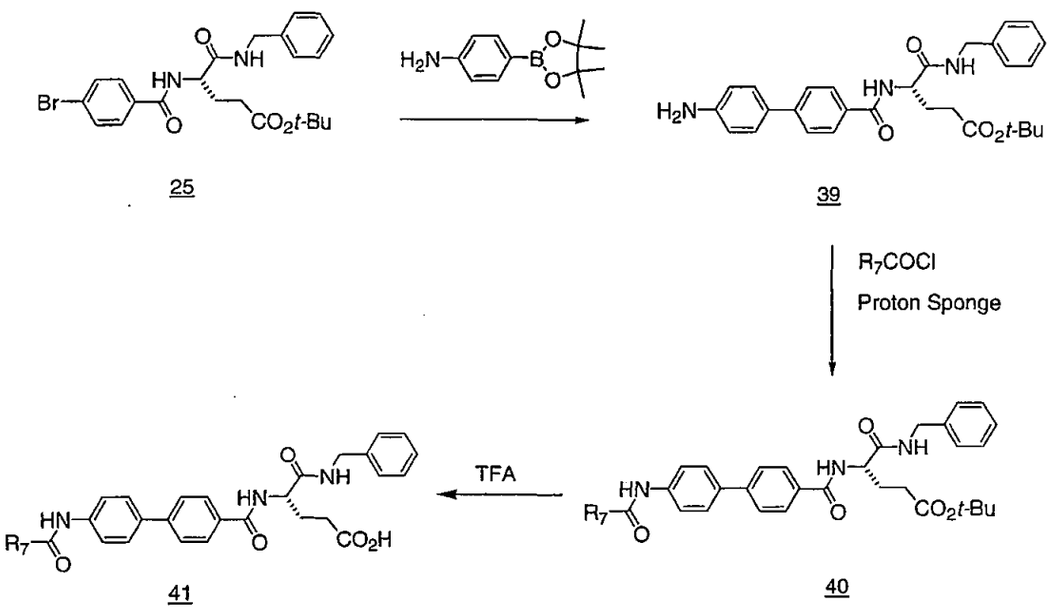


37 38

[0123] Scheme 13 provides compounds of the invention prepared according to the procedure described in scheme 10, except 4-(4,4,5,5)-tetramethyl-1,3,2-dioxoborolan-2-yl)aniline was used in the Suzuki coupling reaction with (25). The amino intermediate

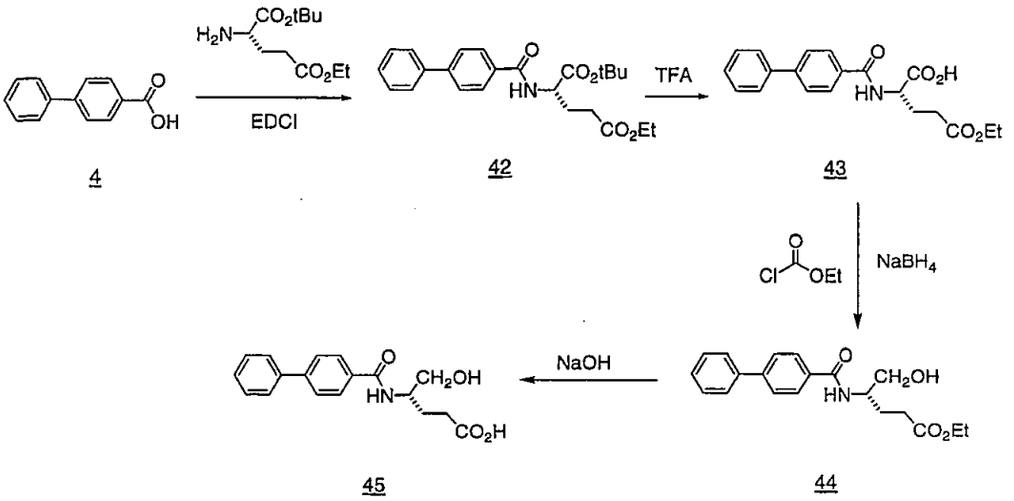
(**39**) was then acylated with an acid chloride and the tert-butyl ester (**40**) was hydrolyzed in acidic conditions to give the desired carboxylic acid (**41**).

Scheme 13



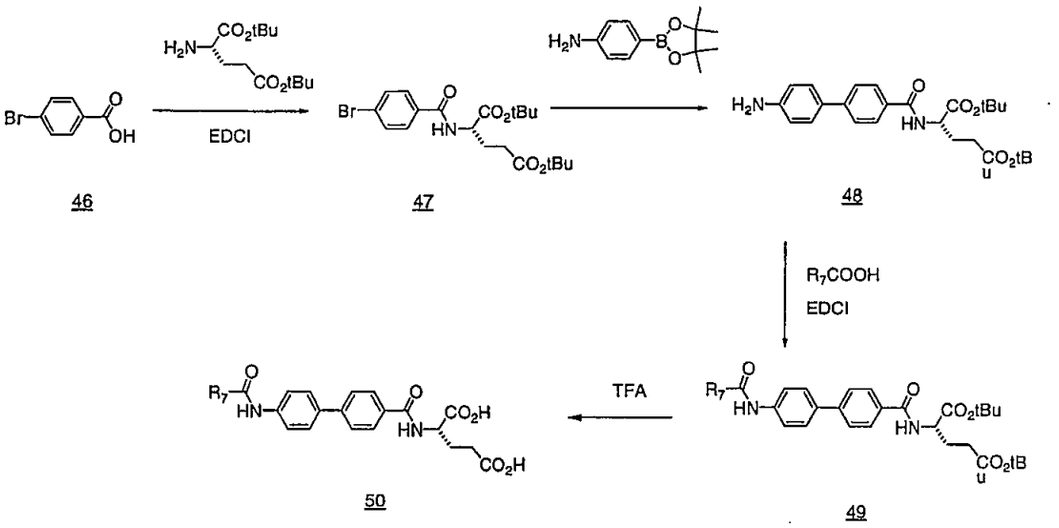
[0124] Scheme 14 demonstrates the preparation of compounds of the invention in four steps. The L-glutamic acid α-tert-butyl ester γ-ethyl ester was reacted with 4-biphenylcarboxylic acid (**4**, or other carboxylic acid) using EDC, PyBop, Bop, or other coupling agent. Hydrolysis of the alpha tert-butyl ester (**42**) in trifluoroacetic acid gave the alpha carboxylic acid intermediate (**43**) in good yield. Treatment of the acid with a base (e.g. triethylamine) and ethyl chloroformate followed by sodium borohydride gave the corresponding alcohol (**44**). The ethyl ester was then hydrolyzed in basic conditions to give the final product (**45**).

Scheme 14



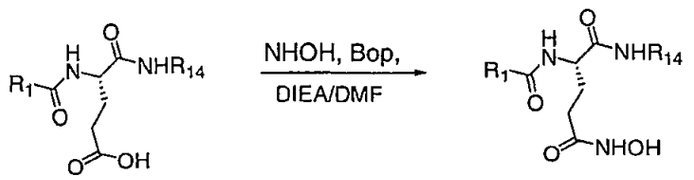
[0125] Scheme 15 provides compounds of the invention prepared in four steps from bromobenzoic acid. L-glutamic acid di-tert butyl ester was coupled with the bromobenzoic acid (**46**). Suzuki coupling of the bromo compound (**47**) with 4-(4,4,5,5)-tetramethyl-1,3,2-dioxoborolan-2-yl)aniline gave the amino intermediate (**48**) in good yield. Acylation of the amine with an acid chloride gave the acylated product (**49**), and hydrolysis of the tert-butyl ester in acidic conditions gave the final dicarboxylic acid (**50**).

Scheme 15



[0126] Scheme 16 provides compounds of the invention prepared in a single step from a carboxylic acid. A carboxylic acid of the invention (17) is reacted with Bop, hydroxylamine hydrochloride, and DIEA to afford the hydroxamic acid (51).

Scheme 16



17 51

[0127] One of skill in the art will recognize that Schemes 1-16 can be adapted to produce other compounds and pharmaceutically acceptable salts of compounds according to the present invention.

Therapeutic Administration

[0128] When administered to an animal, the compounds or pharmaceutically acceptable salts of the compounds of the invention can be administered neat or as a component of a composition that comprises a physiologically acceptable carrier or vehicle. A composition of the invention can be prepared using a method comprising admixing the compound or a pharmaceutically acceptable salt of the compound and a physiologically acceptable carrier, excipient, or diluent. Admixing can be accomplished using methods well known for admixing a compound or a pharmaceutically acceptable salt of the compound and a physiologically acceptable carrier, excipient, or diluent.

[0129] The present compositions, comprising compounds or pharmaceutically acceptable salts of the compounds of the invention can be administered orally. The compounds or pharmaceutically acceptable salts of compounds of the invention can also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral, rectal, vaginal, and intestinal mucosa, etc.) and can be administered together with another therapeutic agent. Administration can be systemic or local. Various known delivery

systems, including encapsulation in liposomes, microparticles, microcapsules, and capsules, can be used.

[0130] Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. In some instances, administration will result of release of the compound or a pharmaceutically acceptable salt of the compound into the bloodstream. The mode of administration is left to the discretion of the practitioner.

[0131] In one embodiment, the compound or a pharmaceutically acceptable salt of the compound is administered orally.

[0132] In another embodiment, the compound or a pharmaceutically acceptable salt of the compound is administered intravenously.

[0133] In another embodiment, it may be desirable to administer the compound or a pharmaceutically acceptable salt of the compound locally. This can be achieved, for example, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository or edema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

[0134] In certain embodiments, it can be desirable to introduce the compound or a pharmaceutically acceptable salt of the compound into the central nervous system, circulatory system or gastrointestinal tract by any suitable route, including intraventricular, intrathecal injection, paraspinal injection, epidural injection, enema, and by injection adjacent to the peripheral nerve. Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

[0135] Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, the compound or a pharmaceutically acceptable salt of the compound can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

[0136] In another embodiment, the compound or a pharmaceutically acceptable salt of the compound can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 1990, 249, 1527-1533 and Treat et al., *Liposomes in the Therapy of Infectious Disease and Cancer* 1989, 317-327 and 353-365.

[0137] In yet another embodiment, the compound or a pharmaceutically acceptable salt of the compound can be delivered in a controlled-release system or sustained-release system (*see, e.g.*, Goodson, in *Medical Applications of Controlled Release* 1984, vol. 2, 115-138). Other controlled or sustained-release systems discussed in the review by Langer, *Science* 1990, 249, 1527-1533 can be used. In one embodiment, a pump can be used (Langer, *Science* 1990, 249, 1527-1533; Sefton, *CRC Crit. Ref. Biomed. Eng.* 1987, 14, 201; Buchwald et al., *Surgery* 1980, 88, 507; and Saudek et al., *N. Engl. J Med.* 1989, 321, 574). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release* (Langer and Wise, eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball, eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 1983, 2, 61; Levy et al., *Science* 1935, 228, 190; During et al., *Ann. Neural.* 1989, 25, 351; and Howard et al., *J. Neurosurg.* 1989, 71, 105).

[0138] In yet another embodiment, a controlled- or sustained-release system can be placed in proximity of a target of the compound or a pharmaceutically acceptable salt of the compound, *e.g.*, the reproductive organs, thus requiring only a fraction of the systemic dose.

[0139] The present compositions can optionally comprise a suitable amount of a physiologically acceptable excipient.

[0140] Such physiologically acceptable excipients can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The physiologically acceptable excipients can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment the physiologically acceptable excipients are sterile when administered to an animal. The physiologically acceptable excipient should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms. Water is a

particularly useful excipient when the compound or a pharmaceutically acceptable salt of the compound is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable physiologically acceptable excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[0141] Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups, and elixirs. The compound or pharmaceutically acceptable salt of the compound of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both, or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives including solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particular containing additives as above, *e.g.*, cellulose derivatives, including sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, *e.g.*, glycols) and their derivatives, and oils (*e.g.*, fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

[0142] The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule. Other examples of suitable physiologically acceptable excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro, ed., 19th ed. 1995).

[0143] In one embodiment, the compound or a pharmaceutically acceptable salt of the compound is formulated in accordance with routine procedures as a composition adapted for oral administration to humans. Compositions for oral delivery can be in the form of tablets, lozenges, buccal forms, troches, aqueous or oily suspensions or solutions, granules, powders, emulsions, capsules, syrups, or elixirs for example. Orally administered compositions can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. In powders, the carrier can be a finely divided solid, which is an admixture with the finely divided compound or pharmaceutically acceptable salt of the compound. In tablets, the compound or pharmaceutically acceptable salt of the compound is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets can contain up to about 99% of the compound or pharmaceutically acceptable salt of the compound.

[0144] Capsules may contain mixtures of the compounds or pharmaceutically acceptable salts of the compounds with inert fillers and/or diluents such as pharmaceutically acceptable starches (*e.g.*, corn, potato, or tapioca starch), sugars, artificial sweetening agents, powdered celluloses (such as crystalline and microcrystalline celluloses), flours, gelatins, gums, etc.

[0145] Tablet formulations can be made by conventional compression, wet granulation, or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents (including, but not limited to, magnesium stearate, stearic acid, sodium lauryl sulfate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, microcrystalline cellulose, sodium carboxymethyl cellulose, carboxymethylcellulose calcium, polyvinylpyrroldine, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, low melting waxes, and ion exchange resins. Surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate,

cetostearl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine.

[0146] Moreover, when in a tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract, thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound or a pharmaceutically acceptable salt of the compound are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule can be imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment the excipients are of pharmaceutical grade.

[0147] In another embodiment, the compound or a pharmaceutically acceptable salt of the compound can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can optionally include a local anesthetic such as lignocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water-free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where the compound or a pharmaceutically acceptable salt of the compound is to be administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the compound or a pharmaceutically acceptable salt of the compound is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

[0148] In another embodiment, the compound or pharmaceutically acceptable salt of the compound can be administered transdermally thorugh the use of a transdermal

patch. Transdermal administrations include administrations across the surface of the body and the inner linings of the bodily passages including epithelial and mucosal tissues. Such administrations can be carried out using the present compounds or pharmaceutically acceptable salts of the compounds, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (*e.g.*, rectal or vaginal).

[0149] Transdermal administration can be accomplished through the use of a transdermal patch containing the compound or pharmaceutically acceptable salt of the compound and a carrier that is inert to the compound or pharmaceutically acceptable salt of the compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams or ointments, pastes, gels, or occlusive devices. The creams or ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the compound or pharmaceutically acceptable salt of the compound into the blood stream, such as a semi-permeable membrane covering a reservoir containing the compound or pharmaceutically acceptable salt of the compound with or without a carrier, or a matrix containing the active ingredient.

[0150] The compounds or pharmaceutically acceptable salts of the compounds of the invention may be administered rectally or vaginally in the form of a conventional suppository. Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water-soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

[0151] The compound or a pharmaceutically acceptable salt of the compound can be administered by controlled-release or sustained-release means or by delivery devices that are known to those of ordinary skill in the art. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those skilled

in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

[0152] In one embodiment a controlled- or sustained-release composition comprises a minimal amount of the compound or a pharmaceutically acceptable salt of the compound to treat or prevent a metalloproteinase-related disorder in a minimal amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased compliance by the animal being treated. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the compound or a pharmaceutically acceptable salt of the compound, and can thus reduce the occurrence of adverse side effects.

[0153] Controlled- or sustained-release compositions can initially release an amount of the compound or a pharmaceutically acceptable salt of the compound that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the compound or a pharmaceutically acceptable salt of the compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the compound or a pharmaceutically acceptable salt of the compound in the body, the compound or a pharmaceutically acceptable salt of the compound can be released from the dosage form at a rate that will replace the amount of the compound or a pharmaceutically acceptable salt of the compound being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

[0154] In certain embodiments, the present invention is directed to prodrugs of the compounds or pharmaceutically acceptable salts of compounds of the present invention. Various forms of prodrugs are known in the art, for example as discussed in Bundgaard, ed., *Design of Prodrugs*, Elsevier (1985); Widder et al., ed., *Methods in Enzymology*, vol. 4, Academic Press (1985); Kgrogsgaard-Larsen et al., ed., *"Design and Application of*

Prodrugs", Textbook of Drug Design and Development, Chapter 5, 113-191 (1991); Bundgaard et al., *Journal of Drug Delivery Reviews* 1992, 8, 1-38; Bundgaard et al., *J. Pharmaceutical Sciences* 1988, 77, 285 et seq.; and Higuchi and Stella, eds., *Prodrugs as Drug Delivery Systems*, American Chemical Society (1975).

[0155] The amount of the compound or a pharmaceutically acceptable salt of the compound is an amount that is effective for treating or preventing a metalloproteinase-related disorder. In addition, *in vitro* or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed can also depend on the route of administration, the condition, the seriousness of the condition being treated, as well as various physical factors related to the individual being treated, and can be decided according to the judgment of a health-care practitioner. Equivalent dosages may be administered over various time periods including, but not limited to, about every 2 hours, about every 6 hours, about every 8 hours, about every 12 hours, about every 24 hours, about every 36 hours, about every 48 hours, about every 72 hours, about every week, about every two weeks, about every three weeks, about every month, and about every two months. The number and frequency of dosages corresponding to a completed course of therapy will be determined according to the judgment of a health-care practitioner. The effective dosage amounts described herein refer to total amounts administered; that is, if more than one compound or a pharmaceutically acceptable salt of the compound is administered, the effective dosage amounts correspond to the total amount administered.

[0156] The amount of the compound or a pharmaceutically acceptable salt of the compound that is effective for treating or preventing a metalloproteinase-related disorder will typically range from about 0.001 mg/kg to about 250 mg/kg of body weight per day, in one embodiment, from about 1 mg/kg to about 250 mg/kg body weight per day, in another embodiment, from about 1 mg/kg to about 50 mg/kg body weight per day, and in another embodiment, from about 1 mg/kg to about 20 mg/kg of body weight per day.

[0157] In one embodiment, the pharmaceutical composition is in unit dosage form, *e.g.*, as a tablet, capsule, powder, solution, suspension, emulsion, granule, or suppository. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet

itself, or it can be the appropriate number of any such compositions in package form. Such unit dosage form may contain from about 1 mg/kg to about 250 mg/kg, and may be given in a single dose or in two or more divided doses.

[0158] The compound or a pharmaceutically acceptable salt of the compound can be assayed *in vitro* or *in vivo* for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

[0159] Thus, in one embodiment, the invention provides a composition comprising an effective amount of the compound or a pharmaceutically acceptable salt of the compound of the present invention and a pharmaceutically acceptable carrier.

[0160] In another embodiment, the pharmaceutically acceptable carrier is suitable for oral administration and the composition comprises an oral dosage form.

Therapeutic or Prophylactic Uses

[0161] In one embodiment, the compounds or pharmaceutically acceptable salts of the compounds of the present invention are useful as metalloproteinase modulators. Accordingly, the compounds and pharmaceutically acceptable salts of the compounds of the present invention are useful for treating an animal with a metalloproteinase-related disorder.

[0162] In one embodiment, the invention provides a method for treating a metalloproteinase-related disorder, comprising administering to an animal in need thereof a compound or a pharmaceutically acceptable salt of the compound of Formula (I) or Formula (II) in an amount effective to treat a metalloproteinase-related disorder. In another embodiment, the compound or pharmaceutically acceptable salt of the compound is of the Formula (Ia), (Ib), (Ic), or (Id).

[0163] In one embodiment, the metalloproteinase is a matrix metalloproteinase or an aggrecanase.

[0164] In another embodiment, the aggrecanase is aggrecanase-1 or aggrecanase-2.

[0165] In one embodiment, the metalloproteinase-related disorder is selected from the group consisting of arthritic disorders, osteoarthritis, cancer, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, atherosclerosis, age-related macular degeneration, myocardial infarction, corneal ulceration and other ocular surface diseases,

hepatitis, aortic aneurysms, tendonitis, central nervous system diseases, abnormal wound healing, angiogenesis, restenosis, cirrhosis, multiple sclerosis, glomerulonephritis, graft versus host disease, diabetes, inflammatory bowel disease, shock, invertebral disc degeneration, stroke, osteopenia, and periodontal diseases.

[0166] In another embodiment, the metalloproteinase-related disorder is osteoarthritis.

[0167] In one embodiment, the present invention is directed to a method for modulating the activity of a metalloproteinase in an animal in need thereof, comprising contacting the metalloproteinase with an effective amount of a compound or pharmaceutically acceptable salt of the compound of Formula (I) or Formula (II). In one embodiment, the method further comprises determining the activity of the metalloproteinase. In one embodiment, the step of determining the activity of the metalloproteinase is performed before the step of contacting the metalloproteinase with the compound or a pharmaceutically acceptable salt of the compound. In another embodiment, the step of determining the activity of the metalloproteinase is performed after the step of contacting the metalloproteinase with the compound or a pharmaceutically acceptable salt of the compound. In another embodiment, the compound or pharmaceutically acceptable salt of the compound is of the Formula (Ia), (Ib), (Ic), or (Id).

[0168] The compounds and pharmaceutically acceptable salts of the compounds of Formula (I) or Formula (II) are also useful in the manufacture of medicaments for treating a metalloproteinase-related disorder in an animal. In another embodiment, the compound or pharmaceutically acceptable salt of the compound is of the Formula (Ia), (Ib), (Ic), or (Id).

[0169] Accordingly, in one embodiment, the invention provides the use of a compound or pharmaceutically acceptable salt of the compound of Formula (I) or Formula (II) for the manufacture of a medicament for treating a metalloproteinase-related disorder. In another embodiment, the compound or pharmaceutically acceptable salt of the compound is of the Formula (Ia), (Ib), (Ic), or (Id).

[0170] In one embodiment, the metalloproteinase is a matrix metalloproteinase or an aggrecanase.

[0171] In another embodiment, the aggrecanase is aggrecanase-1 or aggrecanase-2.

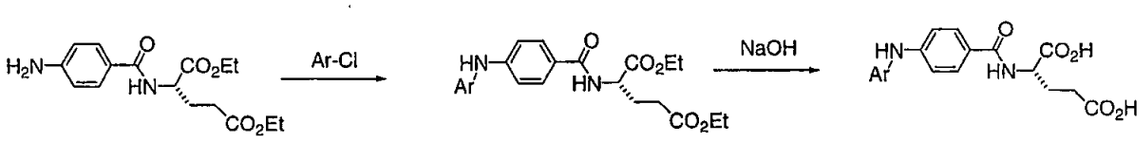
[0172] In one embodiment, the metalloproteinase-related disorder is selected from the group consisting of arthritic disorders, osteoarthritis, cancer, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, atherosclerosis, age-related macular degeneration, myocardial infarction, corneal ulceration and other ocular surface diseases, hepatitis, aortic aneurysms, tendonitis, central nervous system diseases, abnormal wound healing, angiogenesis, restenosis, cirrhosis, multiple sclerosis, glomerulonephritis, graft versus host disease, diabetes, inflammatory bowel disease, shock, invertebral disc degeneration, stroke, osteopenia, and periodontal diseases.

[0173] In another embodiment, the metalloproteinase-related disorder is osteoarthritis.

[0174] In one embodiment, the present invention is directed to the use of a compound or pharmaceutically acceptable salt of the compound of Formula (I) or Formula (II) for the manufacture of a medicament for modulating the activity of a metalloproteinase. In one embodiment, the medicament is also for determining the activity of the receptor. In another embodiment, the compound or pharmaceutically acceptable salt of the compound is of the Formula (Ia), (Ib), (Ic), or (Id).

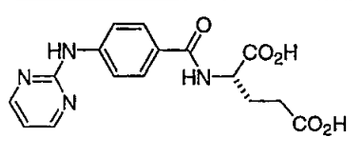
Examples

Scheme 1



1 2 3

Example 1: *N*-[4-(pyrimidin-2-ylamino)benzoyl]-L-glutamic acid



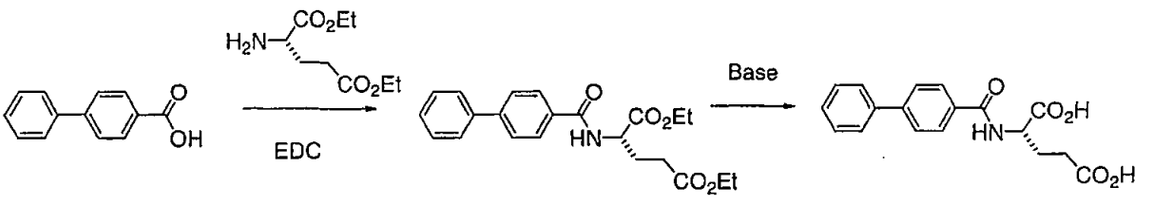
[0175] Step A: 2-[4-(pyrimidin-2-ylamino)-benzoylamino]-pentanedioic acid diethyl ester

2-Chloropyrimidine (0.72 g, 6.3 mmol) and N-(4-aminobenzoyl)-L-glutamic acid diethyl ester (2.04 g, 6.3 mmol, 1 equiv.) were dissolved in DMF (4 mL) and the resulting mixture was heated to 110 °C for 3 hrs. Reaction was complete as determined by TLC. The mixture was cooled to room temperature and partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated by rotavap. The residue was purified by column chromatography (silica gel, 50% EtOAc/hexane) to afford 1.75 g of desired product 2-[4-(pyrimidin-2-ylamino)-benzoylamino]-pentanedioic acid diethyl ester in 69% yield. MS (ESI) *m/z* 399.

[0176] Step B: N-[4-(pyrimidin-2-ylamino)benzoyl]-L-glutamic acid

A solution of 2-[4-(pyrimidin-2-ylamino)-benzoylamino]-pentanedioic acid diethyl ester (250 mg, 0.62 mmol) in THF (4 mL) was added to MeOH (4 mL), followed by the addition of 1N NaOH solution (5 mL, 5 mmol, 8 equiv.). The mixture was stirred at room temperature overnight. Reaction was complete as determined by HPLC. Solvents were removed by rotavap and a small amount of water (5 mL) was added to make a homogeneous solution. 1N HCl was added dropwise until the solution reached a pH of 4. The solid precipitate was collected by filtration, washed with EtOAc, and dried in vacuum oven. The product N-[4-(pyrimidin-2-ylamino)benzoyl]-L-glutamic acid (120 mg) was isolated in 45% yield. MS (ESI) *m/z* 343.

Scheme 2



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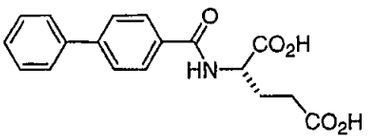
Example 2: N-(1,1'-biphenyl-4-ylcarbonyl)-D-glutamic acid



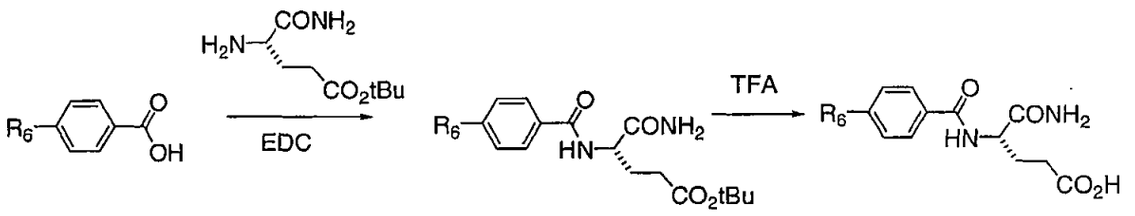
[0177] Step A: 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid diethyl ester

A solution of 4-biphenylcarboxylic acid (670 mg, 3.4 mmol) and (809 mg, 3.4 mmol, 1 equiv.) in dry DMF (20 mL) was added to EDCI (801 mg, 5.1 mmol, 1.5 equiv.), triethylamine (853 mg, 8.4 mmol, 2.5 equiv.) and DMAP (82 mg, 0.7 mmol, 20%). The mixture was stirred at room temperature overnight. Reaction was complete as determined by TLC. The mixture was diluted with EtOAc and washed with H_2O, brine, and dried over magnesium sulfate. Solvent was removed and the residue subject to column chromatography (silica gel, 50% EtOAc/hexane). 660 mg of desired product 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid diethyl ester was isolated in 51% yield. MS (ESI) *m/z* 382.

[0178] Step B: N-(1,1'-biphenyl-4-ylcarbonyl)-D-glutamic acid

A solution of 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid diethyl ester (250 mg, 0.65 mmol) in THF (6 mL) was added to MeOH (6 mL), followed by the addition of 1N NaOH solution (5.2 mL, 5.2 mmol, 8 eq.). The mixture was stirred at room temperature overnight. Reaction was complete as determined by HPLC. Solvents were removed by rotavap and a small amount of water (5 mL) was added to make a homogeneous solution. 1N HCl was added dropwise until the solution reached a pH of 4. The solid precipitate was collected by filtration, washed with EtOAc, and dried in vacuum oven. Product N-(1,1'-biphenyl-4-ylcarbonyl)-D-glutamic acid (189 mg) was isolated in 89% yield. MS (ESI) *m/z* 326.

Scheme 3



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Example 3: N^2-[4-(pyrimidin-2-ylamino)benzoyl]-L-alpha-glutamine

[0179] Step A: 4-Carbamoyl-4-[4-(pyrimidin-2-ylamino)-benzoylamino]-butyric acid tert-butyl ester

4-(Pyrimidin-2-ylamino)-benzoic acid (1.80 g, 8.4 mmol, 1 equiv.) and EDCI (2.41 g, 12.6 mmol, 1.5 equiv.) were dissolved in DMF (60 mL) under N_2. The mixture was stirred at room temperature for 20 minutes, followed by the addition of H-Glu (OtBu)-

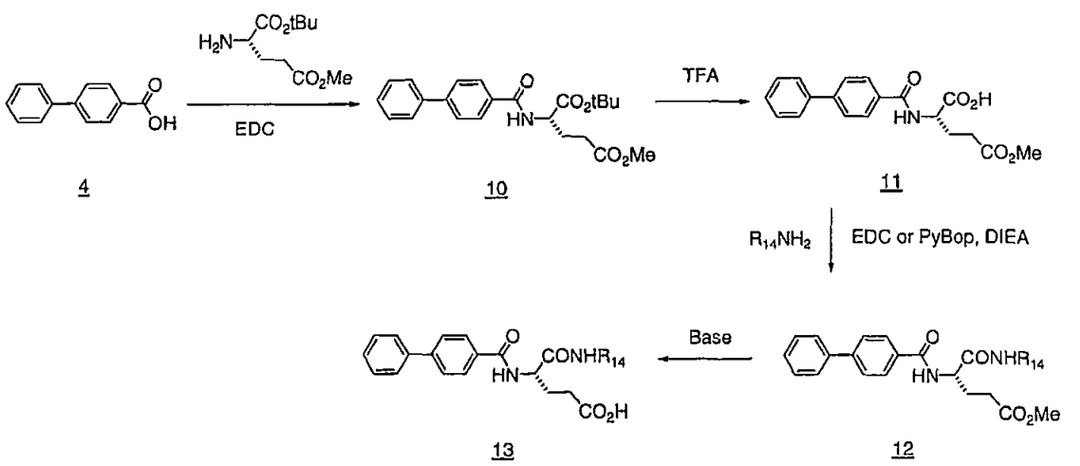
NH_2 (2 g, 8.4 mmol, 1 equiv), Et_3N (2.92 mL, 20.9 mmol, 2.5 equiv.), and DMAP (0.512 g, 4.2 mmol, 0.5 equiv). The mixture was allowed to stir at room temperature overnight. Reaction was complete as determined by TLC. DMF was removed by rotovap and the residue was dissolved in EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Most of the solvent was removed by rotavap and a solid was precipitated from the mixture during solvent evaporation. The solid was collected by filtration and washed with EtOAc. 823 mg of 4-Carbamoyl-4-[4-(pyrimidin-2-ylamino)-benzoylamino]-butyric acid tert-butyl ester was obtained in 25 % yield. MS (ESI) *m/z* 400.

[0180] Step B: N^2-[4-(pyrimidin-2-ylamino)benzoyl]-L-alpha-glutamine 4-Carbamoyl-4-[4-(pyrimidin-2-ylamino)-benzoylamino]-butyric acid tert-butyl ester was dissolved in dichloroethane (10 mL), followed by the addition of TFA (5 mL). The mixture was stirred at room temperature for 4 hrs. TLC indicated the reaction was complete. Solvents were then removed by rotavap and the residue was washed with EtOAc. A solid was collected by filtration and dried in vacuum oven overnight. 4-Carbamoyl-4-[4-(pyrimidin-2-ylamino)-benzoylamino]-butyric acid was obtained in quantitative yield (285 mg). MS (ESI) *m/z* 344.

Example 4: N^2-(1,1'-biphenyl-4-ylcarbonyl)-D-alpha-glutamine

[0181] The title compound was prepared according to the procedures similar to that described for Example 3. Yield 95%, MS (ESI) *m/z* 327.

Scheme 5



Example 5: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-hydroxybutyl)-L-alpha-glutamine

[0182] Step A: 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid 1-tert-butyl ester 5-methyl ester

A solution of 4-diphenyl carboxylic acid (3.57 g, 18 mmol, 1.0 equiv.) in DMF (40 mL) was added to EDCI (4.28 g, 22.3 mmol, 1.24 equiv.) and stirred at room temperature for 0.5 hrs. H-Glu(OMe)Ot-Bu (5.02 g, 19.8 mmol, 1.1 equiv.) was added, followed by the addition of Et_3N (6.77 mL, 48.6 mmol, 2.7 equiv.) and DMAP (330 mg, 2.7 mmol, 15%). The mixture was stirred overnight under N_2. Reaction was complete as determined by TLC. The reaction mixture was diluted with EtOAc, washed with H_2O, then brine solution. The organic layer was separated and then dried over $MgSO_4$. After concentration, crude was purified by column chromatography (Silica gel, 20% EtOAc / Hexane) to afford 3.2 g of 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid 1-tert-butyl ester 5-methyl ester in 44.7% yield. MS (ESI) *m/z* 396.

[0183] Step B: 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid 5-methyl ester

A solution of 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid 1-tert-butyl ester 5-methyl ester (1.5 g, 3.8 mmol) in dichloroethane (26 mL) was added to TFA (13 mL) at room temperature. The mixture was stirred for 4 hrs. and TLC indicated the reaction was complete. Solvent was removed by rotovap. The solid thus obtained was dried under vacuum to provide 1.128 g of 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid 5-methyl ester [G9591-161-1] in 87% yield. MS (ESI) *m/z* 342.

[0184] Step C: 4-[(Biphenyl-4-carbonyl)-amino]-4-(4-hydroxy-butylcarbamoyl)-butyric acid methyl ester

A solution of 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid 5-methyl ester (400 mg, 1.2 mmol, 1 equiv.) in DMF (10 mL) was added to EDCI (337 mg, 1.8 mmol, 1.5 equiv.). The solution was stirred at room temperature under N_2 for 40 min. 4-Amino-1-butanol (0.11 mL, 1.2 mmol, 1 equiv.) was added, followed by addition of Et_3N (0.41 mL, 2.9 mmol, 2.5 equiv.) and DMAP (72 mg, 0.59 mmol, 0.5 equiv.). The mixture was stirred overnight under N_2. The reaction mixture was then poured into cold water and a solid precipitated from the solution. The solid was collected by filtration and dried under vacuum to give 229 mg of 4-[(Biphenyl-4-carbonyl)-amino]-4-(4-hydroxy-butylcarbamoyl)-butyric acid methyl ester in 47% yield.

MS (ESI) *m/z* 413.

[0185] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-hydroxybutyl)-L-alpha-glutamine

A solution of 4-[(Biphenyl-4-carbonyl)-amino]-4-(4-hydroxy-butylcarbamoyl)-butyric acid methyl ester (229 mg, 0.56 mmol, 1 equiv.) in THF (10 mL) and MeOH (2.8 mL) was added to 1N NaOH (2.8 mL, 2.8 mmol, 5 equiv.). The solution was stirred at room temperature for 2.5 hrs. After TLC indicated the reaction was complete, the solvent was evaporated and the residue was dissolved in H_2O. After adjusting the pH of the solution to 3 using 1N HCl, a solid precipitated from the solution. The solid was collected by filtration and washed with water. After drying, 120 mg of N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-hydroxybutyl)-L-alpha-glutamine was isolated in 54.1% yield. MS (ESI) *m/z* 399.

Example 6:

[0186] The following compounds were prepared according to the procedures similar to those described in Example 5.

Example 6A: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-2,3-dihydro-1H-inden-2-yl-L-α-glutamine

[0187] Step C: methyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-2,3-dihydro-1H-inden-2-yl-L-α-glutaminate

Described as above according to the procedure in Example 5, except PyBop/DIEA (or Bop/DIEA) was used. MS (ESI) m/z 457.2; MS (ESI) m/z 913.4; HRMS: calcd for $C_{28}H_{28}N_2O_4$ + H+, 457.21218; found (ESI-FTMS, $[M+H]^{1+}$), 457.21403.

[0188] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-2,3-dihydro-1H-inden-2-yl-L-α-glutamine

MS (ESI) m/z 441.2; MS (ESI) m/z 883.3; HRMS: calcd for $C_{27}H_{26}N_2O_4$ + H+, 443.19653; found (ESI-FTMS, $[M+H]^{1+}$), 443.19699.

Example 6B: N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-hydroxy-1,1-dimethylethyl)-L-α-glutamine

[0189] Step C: methyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-hydroxy-1,1-dimethylethyl)-L-α-glutaminate

Described as above according to the procedure in Example 5, except PyBop/DIEA (or Bop/DIEA) was used. MS (ESI) m/z 413.1; MS (ESI) m/z 825.2; HRMS: calcd for $C_{23}H_{28}N_2O_5$ + H+, 413.20710; found (ESI-FTMS, $[M+H]^{1+}$), 413.20705.

[0190] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-hydroxy-1,1-dimethylethyl)-L-α-glutamine

MS (ESI) m/z 399.1; MS (ESI) m/z 797.3; HRMS: calcd for $C_{22}H_{26}N_2O_5$ + H+, 399.19145; found (ESI-FTMS, $[M+H]^{1+}$), 399.19217.

Example 6C: N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1,3,3-tetramethylbutyl)-L-α-glutamine

[0191] Step C: methyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1,3,3-tetramethylbutyl)-L-α-glutaminate

Described as above according to the procedure in Example 5, except PyBop/DIEA (or Bop/DIEA) was used. MS (ESI) m/z 453.2; MS (ESI) m/z 905.4; HRMS: calcd for $C_{27}H_{36}N_2O_4$ + H+, 453.27478; found (ESI-FTMS, $[M+H]^{1+}$), 453.27588.

[0192] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1,3,3-tetramethylbutyl)-L-α-glutamine

MS (ESI) m/z 439.2; MS (ESI) m/z 877.4; HRMS: calcd for $C_{26}H_{34}N_2O_4$ + H+, 439.25913; found (ESI-FTMS, $[M+H]^{1+}$), 439.25974.

Example 6D: N^1-(1,1-dimethyl-2-phenylethyl)-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine

[0193] Step A: 1-tert-butyl 5-methyl-N-(9H-fluoren-2-ylcarbonyl)-L-glutamate

Described as above according to the procedure in Example 5, except 2-fluorenecarboxylic acid was used. MS (ESI) m/z 410.2; MS (ESI) m/z 819.4; HRMS: calcd for $C_{24}H_{27}NO_5$ + Na+, 432.17814; found (ESI-FTMS, $[M+Na]^{1+}$), 432.17902.

[0194] Step B: (2S)-2-[(9H-fluoren-2-ylcarbonyl)amino]-5-methoxy-5-oxopentanoic acid

MS (ESI) m/z 354.1; MS (ESI) m/z 707.3; HRMS: calcd for $C_{20}H_{19}NO_5$ + H+, 354.13360; found (ESI-FTMS, $[M+H]^{1+}$), 354.13428.

[0195] Step C: methyl N^1-(1,1-dimethyl-2-phenylethyl)-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutaminate

MS (ESI) m/z 485.3; MS (ESI) m/z 969.5; MS (ESI) m/z 507.3; HRMS: calcd for $C_{30}H_{32}N_2O_4$ + Na+, 507.22543; found (ESI-FTMS, $[M+Na]^{1+}$), 507.22863.

[0196] Step D: N^1-(1,1-dimethyl-2-phenylethyl)-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine

MS (ESI) m/z 471.3; MS (ESI) m/z 941.5.

Example 6E: N^1-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine

[0197] Step A: described as above according to the procedure in Example 5, except 2-fluorenecarboxylic acid was used.

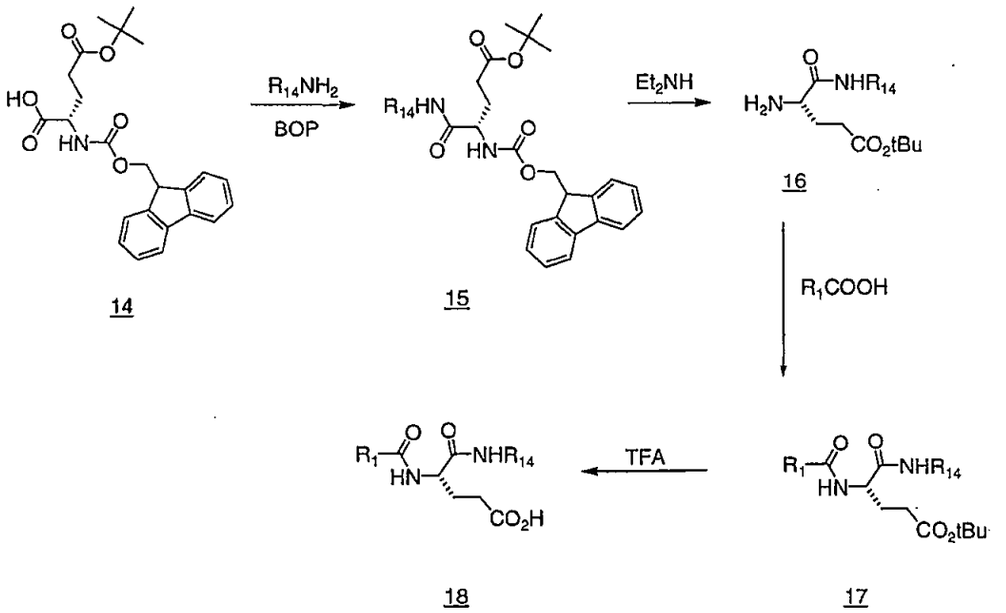
[0198] Step C: methyl N^1-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutaminate

MS (ESI) m/z 519.2; MS (ESI) m/z 1037.5; HRMS: calcd for $C_{30}H_{31}ClN_2O_4$ + H+, 519.20451; found (ESI-FTMS, $[M+H]^{1+}$), 519.20406.

[0199] Step D: N^1-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine

MS (ESI) m/z 505.2; MS (ESI) m/z 1009.5.

Scheme 7



Example 7: N^1-(1,3-benzodioxol-5-ylmethyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

[0200] Step A: *tert*-butyl N^1-(1,3-benzodioxol-5-ylmethyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

In a 50 mL round bottom flask, Fmoc-L-Glu-(OtBu)-OH (2.127 g, 5 mmol) was dissolved in DMF (10 mL) and stirred at room temperature under nitrogen. PyBOP (2.6 g, 5 mmol) was added to the stirring mixture followed by piperonylamine (0.755 g, 5 mmol), and DIEA (1.2 equivalent) added dropwise. The mixture was stirred overnight (18-24 hr) at room temperature under nitrogen. The reaction mixture was then poured into 150 mL of water and the solid was collected and washed with water. The wet solid was then dissolved in ethyl acetate (ca. 500 mL), and washed consecutively with 10% HCl (aq.), $NaHCO_3$ (satd.), and NaCl (satd.). The organic phase was dried over $MgSO_4$ (anh.) and concentrated. The crude product was redissolved in acetone and hexanes were added. The precipitated solid was filtered, washed with hexanes and dried in a vacuum desiccator overnight to give 1.56 g of *tert*-butyl N^1-(1,3-benzodioxol-5-ylmethyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate as fine white solid. MS (ESI) *m/z* 559.1; HRMS: calcd for $C_{32}H_{34}N_2O_7$ + H+, 559.24388; found (ESI_FT, $[M+H]^{1+}$), 559.24348.

[0201] Step B: *tert*-butyl N^1-(1,3-benzodioxol-5-ylmethyl)-L-α-glutaminate

The Fmoc-ester product (1.5 g, 2.7 mmol) was (partially) dissolved in acetonitrile (17 mL) and stirred at room termperature under nitrogen. The mixture was fully dissolved about 30 min after addition of diethylamine (4.2 mL) and was stirred for two hours. After reaction completion, the mixture is carefully concentrated (<30°C) under reduced pressure by rotary evaporator. The crude product (clear oil) was then filtered through a short flash column. The column was gradient eluted starting with 5% Acetone/CH_2Cl_2 until the Fmoc byproduct was removed and ramped to 50% Acetone/CH_2Cl_2 while the product eluted. The desired fractions were collected and concentrated giving 0.8 g clear oil. MS (ESI) *m/z* 337.1; HRMS: calcd for $C_{17}H_{24}N_2O_5$ + H+, 337.17580; found (ESI_FT, $[M+H]^{1+}$), 337.17605.

[0202] Step C: *tert*-butyl N^1-(1,3-benzodioxol-5-ylmethyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutaminate

The free amine (0.36 g, 1.07 mmol) was dissolved in DMF (5 mL) and stirred at rt under

nitrogen. 4-Biphenyl carboxylic acid (0.557 g, 1.07 mmol) was added followed by PyBOP reagent (0.21 g, 1.07 mmol) with vigorous stirring. The reaction mixture was cooled to 0°C and DIEA (1.2 equiv.) was added dropwise. The reaction was complete in 14-24 hours. The reaction mixture was then poured into 100 mL water and the solid collected. The solid was redissolved in ethyl acetate and washed with 10% HCl (aq.), $NaHCO_3$ (satd.), and NaCl (satd.). The organic phase was dried over Na_2SO_4 (anh.) and concentrated. Acetone was added to the residue and diluted with hexanes. The precipitate was collected and dried in a vacuum desiccator overnight to give 0.4 g of desired product. MS (ESI) *m/z* 517.2; HRMS: calcd for $C_{30}H_{32}N_2O_6$ + H+, 517.23331; found (ESI_FT, $[M+H]^{1+}$), 517.23311.

[0203] Step D: N^1-(1,3-benzodioxol-5-ylmethyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

The t-butyl ester (0.31 g, 0.6 mmol) was dissolved in CH_2Cl_2 (4 mL) and stirred at rt under nitrogen. Trifluoroacetic acid (4 mL) dissolved in CH_2Cl_2 (4 mL) is added to the solution and the light yellow solution is stirred at rt for 2 hours. The mixture is evaporated and diluted toluene (10 mL), evaporated to fully remove the TFA. A solid is obtained and dissolved in minimum acetone (ca. 25-50 mL) warmed slightly and hexanes added. The white solid was collected and dried in a vacuum desiccator to yield 0.214 g product. MS (ESI) *m/z* 461.1; HRMS: calcd for $C_{26}H_{24}N_2O_6$ + H+, 461.17071; found (ESI_FT, $[M+H]^{1+}$), 461.1704.

Example 8:

[0204] The following compounds were prepared according to the procedures similar to those of Example 7.

Example 8A: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclohexyl-L-α-glutamine

[0205] Step A: *tert*-butyl N^1-cyclohexyl-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 507.2; HRMS: calcd for $C_{30}H_{38}N_2O_5$ + H+, 507.28535; found (ESI_FT, $[M+H]^{1+}$), 507.28583.

[0206] Step B: *tert*-butyl N^1-cyclohexyl-L-α-glutaminate

MS (ESI) *m/z* 285.2; HRMS: calcd for $C_{15}H_{28}N_2O_3$ + H+, 285.21727; found (ESI_FT,

$[M+H]^{1+}$), 285.21644.

[0207] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclohexyl-L-α-glutaminate

MS (ESI) *m/z* 465.2; HRMS: calcd for $C_{28}H_{36}N_2O_4$ + H+, 465.27478; found (ESI_FT, $[M+H]^{1+}$), 465.27386.

[0208] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclohexyl-L-α-glutamine HRMS: calcd for $C_{24}H_{28}N_2O_4$ + H+, 409.21218; found (ESI_FT, $[M+H]^{1+}$), 409.21163.

Example 8B: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclopropyl-L-α-glutamine

[0209] Step A: *tert*-butyl N^1-cyclopropyl-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 465.1; HRMS: calcd for $C_{27}H_{32}N_2O_5$ + H+, 465.23840; found (ESI_FT, $[M+H]^{1+}$), 465.23816.

[0210] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclopropyl-L-α-glutaminate

MS (ESI) *m/z* 423.2; HRMS: calcd for $C_{25}H_{30}N_2O_4$ + H+, 423.22783; found (ESI_FT, $[M+H]^{1+}$), 423.22725.

[0211] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclopropyl-L-α-glutamine MS (ESI) *m/z* 367.1; MS (ESI) *m/z* 733.2; HRMS: calcd for $C_{21}H_{22}N_2O_4$ + H+, 367.16523; found (ESI_FT, $[M+H]^{1+}$), 367.16454.

Example 8C: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-butyl-L-α-glutamine

[0212] Step A: *tert*-butyl N^1-butyl-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 481.2; MS (ESI) *m/z* 503.2; HRMS: calcd for $C_{28}H_{36}N_2O_5$ + H+, 481.26970; found (ESI_FT, $[M+H]^{1+}$), 481.26789.

[0213] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-butyl-L-α-glutaminate

MS (ESI) *m/z* 439.1; MS (ESI) *m/z* 877.3; HRMS: calcd for $C_{26}H_{34}N_2O_4$ + H+, 439.25913; found (ESI_FT, $[M+H]^{1+}$), 439.25884.

[0214] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-butyl-L-α-glutamine

MS (ESI) *m/z* 381.2; MS (ESI) *m/z* 763.3; HRMS: calcd for $C_{22}H_{26}N_2O_4$ + H+,

383.19653; found (ESI_FT, $[M+H]^{1+}$), 383.19514.

Example 8D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-fluorobenzyl)-L-α-glutamine

[0215] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(4-fluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 533.2; HRMS: calcd for $C_{31}H_{33}FN_2O_5$ + H+, 533.24463; found (ESI_FT, $[M+H]^{1+}$), 533.24546.

[0216] Step B: *tert*-butyl N^1-(4-fluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 311.1; HRMS: calcd for $C_{16}H_{23}FN_2O_3$ + H+, 311.17655; found (ESI_FT, $[M+H]^{1+}$), 311.17696.

[0217] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-fluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 491.2; HRMS: calcd for $C_{29}H_{31}FN_2O_4$ + H+, 491.23406; found (ESI_FT, $[M+H]^{1+}$), 491.23339.

[0218] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-fluorobenzyl)-L-α-glutamine

MS (ESI) *m/z* 435.1; HRMS: calcd for $C_{25}H_{23}FN_2O_4$ + H+, 435.17146; found (ESI_FT, $[M+H]^{1+}$), 435.17056.

Example 8E: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclooctyl-L-α-glutamine

[0219] Step A: *tert*-butyl N^1-cyclooctyl-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 535.2; HRMS: calcd for $C_{32}H_{42}N_2O_5$ + H+, 535.31665; found (ESI_FT, $[M+H]^{1+}$), 535.31782.

[0220] Step B: *tert*-butyl N^1-cyclooctyl-L-α-glutaminate

MS (ESI_FT) *m/z* 313.24821; MS (ESI_FT) *m/z* 313.24857; HRMS: calcd for $C_{17}H_{32}N_2O_3$ + H+, 313.24857; found (ESI_FT, $[M+H]^{1+}$), 313.24821.

[0221] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclooctyl-L-α-glutaminate

MS (ESI) *m/z* 493.4; MS (ESI) *m/z* 985.6; HRMS: calcd for $C_{30}H_{40}N_2O_4$ + H+, 493.30608; found (ESI_FTMS, $[M+H]^{1+}$), 493.30412.

[0222] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclooctyl-L-α-glutamine

MS (ESI) *m/z* 437.3; MS (ESI) *m/z* 873.6; HRMS: calcd for $C_{26}H_{32}N_2O_4$ + H+, 437.24348; found (ESI_FT, $[M+H]^{1+}$), 437.24272.

Example 8F: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethoxybenzyl)-L-α-glutamine

[0223] Step A: *tert*-butyl N^1-(3,4-dimethoxybenzyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 575.3; MS (ESI) *m/z* 1149.6; HRMS: calcd for $C_{33}H_{38}N_2O_7$ + H+, 575.27518; found (ESI_FT, $[M+H]^{1+}$), 575.27609.

[0224] Step B: *tert*-butyl N^1-(3,4-dimethoxybenzyl)-L-α-glutaminate

MS (ESI+) *m/z* 353.2; MS (ESI+) *m/z* 297.1; HRMS: calcd for $C_{18}H_{28}N_2O_5$ + H+, 353.20710; found (ESI_FT, $[M+H]^{1+}$), 353.20629.

[0225] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethoxybenzyl)-L-α-glutaminate

MS (ESI+) *m/z* 533.3; HRMS: calcd for $C_{31}H_{36}N_2O_6$ + H+, 533.26461; found (ESI_FT, $[M+H]^{1+}$), 533.26323.

[0226] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethoxybenzyl)-L-α-glutamine

MS (ESI-) *m/z* 475.3; HRMS: calcd for $C_{27}H_{28}N_2O_6$ + H+, 477.20201; found (ESI_FT, $[M+H]^{1+}$), 477.20053.

Example 8G: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclopentyl-L-α-glutamine

[0227] Step A: *tert*-butyl N^1-cyclopentyl-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI+) *m/z* 493.3; MS (ESI+) *m/z* 437.2; HRMS: calcd for $C_{29}H_{36}N_2O_5$ + H+, 493.26970; found (ESI_FT, $[M+H]^{1+}$), 493.26812.

[0228] Step B: *tert*-butyl N^1-cyclopentyl-L-α-glutaminate

MS (ESI) *m/z* 271.2; HRMS: calcd for $C_{14}H_{26}N_2O_3$ + H+, 271.20162; found (ESI_FT, $[M+H]^{1+}$), 271.202.

[0229] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclopentyl-L-α-glutaminate

MS (ESI) *m/z* 451.3; MS (ESI) *m/z* 901.6; HRMS: calcd for $C_{27}H_{34}N_2O_4$ + H+,

451.25913; found (ESI_FT, $[M+H]^{1+}$), 451.25803.

[0230] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclopentyl-L-α-glutamine

MS (ESI) *m/z* 395.2; MS (ESI) *m/z* 789.4; HRMS: calcd for $C_{23}H_{26}N_2O_4$ + H+, 395.19653; found (ESI_FT, $[M+H]^{1+}$), 395.19564.

Example 8H: N^1-2-adamantyl-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

[0231] Step A: *tert*-butyl N^1-2-adamantyl-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 559.4; MS (ESI) *m/z* 1117.7; HRMS: calcd for $C_{34}H_{42}N_2O_5$ + H+, 559.31665; found (ESI_FT, $[M+H]^{1+}$), 559.31524.

[0232] Step B: *tert*-butyl N^1-2-adamantyl-L-α-glutaminate

MS (ESI) *m/z* 337.2; MS (ESI) *m/z* 673.5; HRMS: calcd for $C_{19}H_{32}N_2O_3$ + H+, 337.24857; found (ESI_FT, $[M+H]^{1+}$), 337.2475.

[0233] Step C: *tert*-butyl N^1-2-adamantyl-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutaminate

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1033.6; HRMS: calcd for $C_{32}H_{40}N_2O_4$ + H+, 517.30608; found (ESI_FT, $[M+H]^{1+}$), 517.30505.

[0234] Step D: N^1-2-adamantyl-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

MS (ESI) *m/z* 461.3; MS (ESI) *m/z* 921.5; HRMS: calcd for $C_{28}H_{32}N_2O_4$ + H+, 461.24348; found (ESI_FT, $[M+H]^{1+}$), 461.24227.

Example 8I: N^1-(2-adamantylmethyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

[0235] Step A: *tert*-butyl N^1-(2-adamantylmethyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 573.3; MS (ESI) *m/z* 1145.5; HRMS: calcd for $C_{35}H_{44}N_2O_5$ + H+, 573.33230; found (ESI_FT, $[M+H]^{1+}$), 573.33089.

[0236] Step B: *tert*-butyl N^1-(2-adamantylmethyl)-L-α-glutaminate

MS (ESI) *m/z* 351.2; HRMS: calcd for $C_{20}H_{34}N_2O_3$ + H+, 351.26422; found (ESI_FT, $[M+H]^{1+}$), 351.26491.

[0237] Step C: *tert*-butyl N^1-(2-adamantylmethyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutaminate

MS (ESI) *m/z* 531.3; MS (ESI) *m/z* 1061.4; HRMS: calcd for $C_{33}H_{42}N_2O_4$ + H+, 531.32173; found (ESI_FT, $[M+H]^{1+}$), 531.32031.

[0238] Step D: N^1-(2-adamantylmethyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

MS (ESI) *m/z* 475.2; MS (ESI) *m/z* 949.3; HRMS: calcd for $C_{29}H_{34}N_2O_4$ + H+, 475.25913; found (ESI_FT, $[M+H]^{1+}$), 475.25734.

Example 8J: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methoxyethyl)-L-α-glutamine

[0239] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(2-methoxyethyl)-L-α-glutaminate

MS (ESI) *m/z* 483.2; MS (ESI) *m/z* 965.3; HRMS: calcd for $C_{27}H_{34}N_2O_6$ + H+, 483.24896; found (ESI_FT, $[M+H]^{1+}$), 483.24851.

[0240] Step B: *tert*-butyl N^1-(2-methoxyethyl)-L-α-glutaminate

MS (ESI) *m/z* 261.1; HRMS: calcd for $C_{12}H_{24}N_2O_4$ + H+, 261.18088; found (ESI_FT, $[M+H]^{1+}$), 261.18071.

[0241] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methoxyethyl)-L-α-glutaminate

MS (ESI) *m/z* 441.2; MS (ESI) *m/z* 881.3; HRMS: calcd for $C_{25}H_{32}N_2O_5$ + H+, 441.23840; found (ESI_FT, $[M+H]^{1+}$), 441.23803.

[0242] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methoxyethyl)-L-α-glutamine

MS (ESI) *m/z* 385.1; MS (ESI) *m/z* 769.2; HRMS: calcd for $C_{21}H_{24}N_2O_5$ + H+, 385.17580; found (ESI_FT, $[M+H]^{1+}$), 385.17538.

Example 8K: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methoxybenzyl)-L-α-glutamine

[0243] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(4-methoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 545.2; MS (ESI) *m/z* 1089.3; HRMS: calcd for $C_{32}H_{36}N_2O_6$ + H+, 545.26461; found (ESI_FT, $[M+H]^{1+}$), 545.26277.

[0244] Step B: *tert*-butyl N^1-(4-methoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 323.2; HRMS: calcd for $C_{17}H_{26}N_2O_4$ + H+, 323.19653; found (ESI_FT, $[M+H]^{1+}$), 323.19702.

[0245] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 503.2; MS (ESI) *m/z* 1005.4; HRMS: calcd for $C_{30}H_{34}N_2O_5$ + H+, 503.25405; found (ESI_FT, $[M+H]^{1+}$), 503.25435.

[0246] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methoxybenzyl)-L-α-glutamine

MS (ESI) *m/z* 445.2; MS (ESI) *m/z* 891.5; HRMS: calcd for $C_{26}H_{26}N_2O_5$ + H+, 447.19145; found (ESI_FT, $[M+H]^{1+}$), 447.19235.

Example 8L: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3,4-dimethoxyphenyl)ethyl]-L-α-glutamine

[0247] Step A: *tert*-butyl N^1-[2-(3,4-dimethoxyphenyl)ethyl]-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 589.2; MS (ESI) *m/z* 1177.3; HRMS: calcd for $C_{34}H_{40}N_2O_7$ + H+, 589.29083; found (ESI_FT, $[M+H]^{1+}$), 589.28932.

[0248] Step B: *tert*-butyl N^1-[2-(3,4-dimethoxyphenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 367.2; HRMS: calcd for $C_{19}H_{30}N_2O_5$ + H+, 367.22275; found (ESI_FT, $[M+H]^{1+}$), 367.22308.

[0249] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3,4-dimethoxyphenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 547.3; MS (ESI) *m/z* 1093.4; HRMS: calcd for $C_{32}H_{38}N_2O_6$ + H+, 547.28026; found (ESI_FT, $[M+H]^{1+}$), 547.280241.

[0250] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3,4-dimethoxyphenyl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 491.2; MS (ESI) *m/z* 981.2; HRMS: calcd for $C_{28}H_{30}N_2O_6$ + H+, 491.21766; found (ESI_FT, $[M+H]^{1+}$), 491.21697.

Example 8M: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(4-methoxyphenyl)ethyl]-L-α-glutamine

[0251] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[2-(4-methoxyphenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 559.2; MS (ESI) *m/z* 1117.3; HRMS: calcd for $C_{33}H_{38}N_2O_6$ + H+,

559.28026; found (ESI_FT, $[M+H]^{1+}$), 559.27899.

[0252] Step B: *tert*-butyl N^1-[2-(4-methoxyphenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 337.1; MS (ESI) *m/z* 673.3; HRMS: calcd for $C_{18}H_{28}N_2O_4$ + H+, 337.21218; found (ESI_FT, $[M+H]^{1+}$), 337.21196.

[0253] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(4-methoxyphenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 517.2; MS (ESI) *m/z* 1033.4; HRMS: calcd for $C_{31}H_{36}N_2O_5$ + H+, 517.26970; found (ESI_FT, $[M+H]^{1+}$), 517.26875.

[0254] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(4-methoxyphenyl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 461.2; MS (ESI) *m/z* 921.3; HRMS: calcd for $C_{27}H_{28}N_2O_5$ + H+, 461.20710; found (ESI_FT, $[M+H]^{1+}$), 461.2062.

Example 8N: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(1-naphthylmethyl)-L-α-glutamine

[0255] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(1-naphthylmethyl)-L-α-glutaminate

MS (ESI) *m/z* 565.2; MS (ESI) *m/z* 1129.4; HRMS: calcd for $C_{35}H_{36}N_2O_5$ + H+, 565.26970; found (ESI_FT, $[M+H]^{1+}$), 565.26849.

[0256] Step B: *tert*-butyl N^1-(1-naphthylmethyl)-L-α-glutaminate

MS (ESI) *m/z* 343.1; MS (ESI) *m/z* 685.3; HRMS: calcd for $C_{20}H_{26}N_2O_3$ + H+, 343.20162; found (ESI_FT, $[M+H]^{1+}$), 343.2014.

[0257] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(1-naphthylmethyl)-L-α-glutaminate

MS (ESI) *m/z* 523.2; MS (ESI) *m/z* 1045.4; HRMS: calcd for $C_{33}H_{34}N_2O_4$ + H+, 523.25913; found (ESI_FT, $[M+H]^{1+}$), 523.2583.

[0258] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(1-naphthylmethyl)-L-α-glutamine

MS (ESI) *m/z* 467.2; MS (ESI) *m/z* 933.3; HRMS: calcd for $C_{29}H_{26}N_2O_4$ + H+, 467.19653; found (ESI_FT, $[M+H]^{1+}$), 467.19528.

Example 8O: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-methylbenzyl)-L-α-glutamine

[0259] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(3-methylbenzyl)-L-α-glutaminate

MS (ESI) *m/z* 529.1; MS (ESI) *m/z* 1057.4; HRMS: calcd for $C_{32}H_{36}N_2O_5$ + H+, 529.26970; found (ESI_FT, $[M+H]^{1+}$), 529.26804.

[0260] Step B: *tert*-butyl N^1-(3-methylbenzyl)-L-α-glutaminate

MS (ESI) *m/z* 307.1; MS (ESI) *m/z* 613.3; HRMS: calcd for $C_{17}H_{26}N_2O_3$ + H+, 307.20162; found (ESI_FT, $[M+H]^{1+}$), 307.20079.

[0261] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-methylbenzyl)-L-α-glutaminate

HRMS: calcd for $C_{30}H_{34}N_2O_4$ + H+, 487.25913; found (ESI_FT, $[M+H]^{1+}$), 487.25842.

[0262] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-methylbenzyl)-L-α-glutamine

HRMS: calcd for $C_{26}H_{26}N_2O_4$ + H+, 431.19653; found (ESI_FT, $[M+H]^{1+}$), 431.19568.

Example 8P: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-furylmethyl)-L-α-glutamine

[0263] Step A: tert-butyl N^2-[(9H-fluoren-9-ylmethoxy)carbonyl]-N^1-(2-furylmethyl)-L-α-glutaminate

MS (ESI) m/z 505.2; HRMS: calcd for $C_{29}H_{32}N_2O_6$ + H+, 505.23331; found (ESI_FT, $[M+H]^{1+}$), 505.23263.

[0264] Step B: tert-butyl N^1-(2-furylmethyl)-L-α-glutaminate

HRMS: calcd for $C_{14}H_{22}N_2O_4$ + H+, 283.16523; found (ESI_FT, $[M+H]^{1+}$), 283.16497.

[0265] Step C: tert-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-furylmethyl)-L-α-glutaminate

HRMS: calcd for $C_{27}H_{30}N_2O_5$ + H+, 463.22275; found (ESI_FT, $[M+H]^{1+}$), 463.22212.

[0266] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-furylmethyl)-L-α-glutamine

HRMS: calcd for $C_{23}H_{22}N_2O_5$ + H+, 407.16015; found (ESI_FT, $[M+H]^{1+}$), 407.15957.

Example 8Q: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-methoxybenzyl)-L-α-glutamine

[0267] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(3-methoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 545.3; MS (ESI) *m/z* 1089.5; HRMS: calcd for $C_{32}H_{36}N_2O_6$ + H+,

545.26461; found (ESI_FT, $[M+H]^{1+}$), 545.26286.

[0268] Step B: *tert*-butyl N^1-(3-methoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 323.3; MS (ESI) *m/z* 645.7; HRMS: calcd for $C_{17}H_{26}N_2O_4$ + H+, 323.19653; found (ESI_FT, $[M+H]^{1+}$), 323.19687.

[0269] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-methoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 503.2; MS (ESI) *m/z* 1005.5; HRMS: calcd for $C_{30}H_{34}N_2O_5$ + H+, 503.25405; found (ESI_FT, $[M+H]^{1+}$), 503.25322.

[0270] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-methoxybenzyl)-L-α-glutamine

MS (ESI) *m/z* 447.2; MS (ESI) *m/z* 893.3; HRMS: calcd for $C_{26}H_{26}N_2O_5$ + H+, 447.19145; found (ESI_FT, $[M+H]^{1+}$), 447.19079.

Example 8R: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0271] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 605.2; MS (ESI) *m/z* 1209.4; HRMS: calcd for $C_{34}H_{40}N_2O_8$ + H+, 605.28574; found (ESI_FT, $[M+H]^{1+}$), 605.28453.

[0272] Step B: *tert*-butyl N^1-(3,4,5-trimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 383.1; MS (ESI) *m/z* 765.3; HRMS: calcd for $C_{19}H_{30}N_2O_6$ + H+, 383.21766; found (ESI_FT, $[M+H]^{1+}$), 383.21755.

[0273] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 563.3; MS (ESI) *m/z* 1125.5; HRMS: calcd for $C_{32}H_{38}N_2O_7$ + H+, 563.27518; found (ESI_FT, $[M+H]^{1+}$); 563.2744.

[0274] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine

MS (ESI) *m/z* 507.2; MS (ESI) *m/z* 1013.4; HRMS: calcd for $C_{28}H_{30}N_2O_7$ + H+, 507.21258; found (ESI_FT, $[M+H]^{1+}$), 507.21179.

Example 8S: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,4-dichlorobenzyl)-L-α-glutamine

[0275] Step A: *tert*-butyl N^1-(2,4-dichlorobenzyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 583.1; HRMS: calcd for $C_{31}H_{32}Cl_2N_2O_5$ + H+, 583.17610; found (ESI_FT, $[M+H]^{1+}$), 583.1742.

[0276] Step B: *tert*-butyl N^1-(2,4-dichlorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 361.1; MS (ESI) *m/z* 721.2; HRMS: calcd for $C_{16}H_{22}Cl_2N_2O_3$ + H+, 361.10802; found (ESI_FT, $[M+H]^{1+}$), 361.10891.

[0277] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,4-dichlorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 541.2; MS (ESI) *m/z* 1081.3; HRMS: calcd for $C_{29}H_{30}Cl_2N_2O_4$ + H+, 541.16554; found (ESI_FT, $[M+H]^{1+}$), 541.16693.

[0278] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,4-dichlorobenzyl)-L-α-glutamine

MS (ESI) *m/z* 483.1; MS (ESI) *m/z* 967.2; HRMS: calcd for $C_{25}H_{22}Cl_2N_2O_4$ + H+, 485.10294; found (ESI_FT, $[M+H]^{1+}$), 485.10231.

Example 8T: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-(trifluoromethoxy)benzyl]-L-α-glutamine

[0279] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[4-(trifluoromethoxy)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 599.1; MS (ESI) *m/z* 1197.3; HRMS: calcd for $C_{32}H_{33}F_3N_2O_6$ + H+, 599.23635; found (ESI_FT, $[M+H]^{1+}$), 599.23521.

[0280] Step B: *tert*-butyl N^1-[4-(trifluoromethoxy)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 377.1; HRMS: calcd for $C_{17}H_{23}F_3N_2O_4$ + H+, 377.16827; found (ESI_FT, $[M+H]^{1+}$), 377.16901.

[0281] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-(trifluoromethoxy)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 557.2; MS (ESI) *m/z* 1113.4; HRMS: calcd for $C_{30}H_{31}F_3N_2O_5$ + H+, 557.22578; found (ESI_FT, $[M+H]^{1+}$), 557.22537.

[0282] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-(trifluoromethoxy)benzyl]-L-α-glutamine

MS (ESI) *m/z* 501.2; MS (ESI) *m/z* 1001.3; HRMS: calcd for $C_{26}H_{23}F_3N_2O_5$ + H+,

501.16318; found (ESI_FT, $[M+H]^{1+}$), 501.16263.

Example 8U: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[3-(trifluoromethoxy)benzyl]-L-α-glutamine

[0283] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[3-(trifluoromethoxy)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 599.2; MS (ESI) *m/z* 1197.4; HRMS: calcd for $C_{32}H_{33}F_3N_2O_6$ + H+, 599.23635; found (ESI_FT, $[M+H]^{1+}$), 599.23596.

[0284] Step B: *tert*-butyl N^1-[3-(trifluoromethoxy)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 377.1; MS (ESI) *m/z* 753.3; HRMS: calcd for $C_{17}H_{23}F_3N_2O_4$ + H+, 377.16827; found (ESI_FT, $[M+H]^{1+}$), 377.1691.

[0285] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[3-(trifluoromethoxy)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 557.2; MS (ESI) *m/z* 1113.4; HRMS: calcd for $C_{30}H_{31}F_3N_2O_5$ + H+, 557.22578; found (ESI_FT, $[M+H]^{1+}$), 557.22558.

[0286] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[3-(trifluoromethoxy)benzyl]-L-α-glutamine

MS (ESI) *m/z* 499.1; MS (ESI) *m/z* 999.3; HRMS: calcd for $C_{26}H_{23}F_3N_2O_5$ + H+, 501.16318; found (ESI_FT, $[M+H]^{1+}$), 501.16265.

Example 8V: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-(methylthio)benzyl]-L-α-glutamine

[0287] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[4-(methylthio)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 561.2; MS (ESI) *m/z* 1121.4; HRMS: calcd for $C_{32}H_{36}N_2O_5S$ + H+, 561.24177; found (ESI_FT, $[M+H]^{1+}$), 561.24183.

[0288] Step B: *tert*-butyl N^1-[4-(methylthio)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 339.2; MS (ESI) *m/z* 677.3; HRMS: calcd for $C_{17}H_{26}N_2O_3S$ + H+, 339.17369; found (ESI_FT, $[M+H]^{1+}$), 339.1748.

[0289] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-(methylthio)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 519.2; MS (ESI) *m/z* 1037.4; HRMS: calcd for $C_{30}H_{34}N_2O_4S$ + H+,

519.23120; found (ESI_FT, $[M+H]^{1+}$), 519.23078.

[0290] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-(methylthio)benzyl]-L-α-glutamine

MS (ESI) *m/z* 461.1; MS (ESI) *m/z* 923.3; HRMS: calcd for $C_{26}H_{26}N_2O_4S$ + H+, 463.16860; found (ESI_FT, $[M+H]^{1+}$), 463.16807.

Example 8W: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-phenoxybenzyl)-L-α-glutamine

[0291] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(4-phenoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 607.3; MS (ESI) *m/z* 1213.5; HRMS: calcd for $C_{37}H_{38}N_2O_6$ + H+, 607.28026; found (ESI_FT, $[M+H]^{1+}$), 607.27904.

[0292] Step B: *tert*-butyl N^1-(4-phenoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 385.2; MS (ESI) *m/z* 769.4; HRMS: calcd for $C_{22}H_{28}N_2O_4$ + H+, 385.21218; found (ESI_FT, $[M+H]^{1+}$), 385.21141.

[0293] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-phenoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 565.3; MS (ESI) *m/z* 1129.5; HRMS: calcd for $C_{35}H_{36}N_2O_5$ + H+, 565.26970; found (ESI_FT, $[M+H]^{1+}$), 565.27062.

[0294] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-phenoxybenzyl)-L-α-glutamine

MS (ESI) *m/z* 507.2; MS (ESI) *m/z* 1015.4; HRMS: calcd for $C_{31}H_{28}N_2O_5$ + H+, 509.20710; found (ESI_FT, $[M+H]^{1+}$), 509.20657.

Example 8X: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3-methoxyphenyl)ethyl]-L-α-glutamine

[0295] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[2-(3-methoxyphenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 559.3; MS (ESI) *m/z* 1117.6; HRMS: calcd for $C_{33}H_{38}N_2O_6$ + H+, 559.28026; found (ESI_FT, $[M+H]^{1+}$), 559.28074.

[0296] Step B: *tert*-butyl N^1-[2-(3-methoxyphenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 337.2; HRMS: calcd for $C_{18}H_{28}N_2O_4$ + H+, 337.21218; found (ESI_FT, $[M+H]^{1+}$), 337.21275.

[0297] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3-methoxyphenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1033.6; HRMS: calcd for $C_{31}H_{36}N_2O_5$ + H+, 517.26970; found (ESI_FT, $[M+H]^{1+}$), 517.27068.

[0298] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3-methoxyphenyl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 461.2; MS (ESI) *m/z* 921.4; HRMS: calcd for $C_{27}H_{28}N_2O_5$ + H+, 461.20710; found (ESI_FT, $[M+H]^{1+}$), 461.20723.

Example 8Y: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,4-dimethoxybenzyl)-L-α-glutamine

[0299] Step A: *tert*-butyl N^1-(2,4-dimethoxybenzyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 575.3; MS (ESI) *m/z* 1149.5; HRMS: calcd for $C_{33}H_{38}N_2O_7$ + H+, 575.27518; found (ESI_FT, $[M+H]^{1+}$), 575.275181.

[0300] Step B: *tert*-butyl N^1-(2,4-dimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 353.2; MS (ESI) *m/z* 705.4; HRMS: calcd for $C_{18}H_{28}N_2O_5$ + H+, 353.20710; found (ESI_FT, $[M+H]^{1+}$), 353.20767.

[0301] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,4-dimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 533.3; MS (ESI) *m/z* 1065.6; HRMS: calcd for $C_{31}H_{36}N_2O_6$ + H+, 533.26461; found (ESI_FT, $[M+H]^{1+}$), 533.26569.

[0302] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,4-dimethoxybenzyl)-L-α-glutamine

MS (ESI) *m/z* 477.2; MS (ESI) *m/z* 953.4; HRMS: calcd for $C_{27}H_{28}N_2O_6$ + H+, 477.20201; found (ESI_FT, $[M+H]^{1+}$), 477.2019.

Example 8Z: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methoxybenzyl)-L-α-glutamine

[0303] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(2-methoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 545.2; HRMS: calcd for $C_{32}H_{36}N_2O_6$ + H+, 545.26461; found (ESI_FT, $[M+H]^{1+}$), 545.26356.

[0304] Step B: *tert*-butyl N^1-(2-methoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 323.2; MS (ESI) *m/z* 645.4; HRMS: calcd for $C_{17}H_{26}N_2O_4$ + H+, 323.19653; found (ESI_FT, $[M+H]^{1+}$), 323.19657.

[0305] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 503.2; MS (ESI) *m/z* 1005.5; HRMS: calcd for $C_{30}H_{34}N_2O_5$ + H+, 503.25405; found (ESI_FT, $[M+H]^{1+}$), 503.2546.

[0306] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methoxybenzyl)-L-α-glutamine

MS (ESI) *m/z* 447.2; MS (ESI) *m/z* 893.4; HRMS: calcd for $C_{26}H_{26}N_2O_5$ + H+, 447.19145; found (ESI_FT, $[M+H]^{1+}$), 447.19143.

Example 8AA: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,5-difluorobenzyl)-L-α-glutamine

[0307] Step A: *tert*-butyl N^1-(3,5-difluorobenzyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 551.2; MS (ESI) *m/z* 1101.4; HRMS: calcd for $C_{31}H_{32}F_2N_2O_5$ + H+, 551.23521; found (ESI_FT, $[M+H]^{1+}$), 551.23338.

[0308] Step B: *tert*-butyl N^1-(3,5-difluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 329.1; MS (ESI) *m/z* 657.3; HRMS: calcd for $C_{16}H_{22}F_2N_2O_3$ + H+, 329.16712; found (ESI_FT, $[M+H]^{1+}$), 329.16762.

[0309] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,5-difluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 509.2; MS (ESI) *m/z* 1017.3; HRMS: calcd for $C_{29}H_{30}F_2N_2O_4$ + H+, 509.22464; found (ESI_FTMS, $[M+H]^{1+}$), 509.22463.

[0310] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,5-difluorobenzyl)-L-α-glutamine

MS (ESI) *m/z* 451.1; MS (ESI) *m/z* 903.3; HRMS: calcd for $C_{25}H_{22}F_2N_2O_4$ + H+, 453.16204; found (ESI_FTMS, $[M+H]^{1+}$), 453.16222.

Example 8BB: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dichlorobenzyl)-L-α-glutamine

[0311] Step A: *tert*-butyl N^1-(3,4-dichlorobenzyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 583.1; MS (ESI) *m/z* 1165.2; HRMS: calcd for $C_{31}H_{32}Cl_2N_2O_5$ + H+, 583.17610; found (ESI_FT, $[M+H]^{1+}$), 583.17528.

[0312] Step B: *tert*-butyl N^1-(3,4-dichlorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 361.1; MS (ESI) *m/z* 721.2; HRMS: calcd for $C_{16}H_{22}Cl_2N_2O_3$ + H+, 361.10802; found (ESI_FT, $[M+H]^{1+}$), 361.10861.

[0313] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dichlorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 541.2; MS (ESI) *m/z* 1081.3; HRMS: calcd for $C_{29}H_{30}Cl_2N_2O_4$ + H+, 541.16554; found (ESI_FT, $[M+H]^{1+}$), 541.16685.

[0314] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dichlorobenzyl)-L-α-glutamine

MS (ESI) *m/z* 483.1; MS (ESI) *m/z* 967.2; HRMS: calcd for $C_{25}H_{22}Cl_2N_2O_4$ + H+, 485.10294; found (ESI_FTMS, $[M+H]^{1+}$), 485.10288.

Example 8CC: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,5-dimethoxybenzyl)-L-α-glutamine

[0315] Step A: *tert*-butyl N^1-(3,5-dimethoxybenzyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 575.3; HRMS: calcd for $C_{33}H_{38}N_2O_7$ + H+, 575.27518; found (ESI_FTMS, $[M+H]^{1+}$), 575.27468.

[0316] Step B: *tert*-butyl N^1-(3,5-dimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 353.2; HRMS: calcd for $C_{18}H_{28}N_2O_5$ + H+, 353.20710; found (ESI_FTMS, $[M+H]^{1+}$), 353.20732.

[0317] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,5-dimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 533.3; MS (ESI) *m/z* 1065.5; HRMS: calcd for $C_{31}H_{36}N_2O_6$ + H+, 533.26461; found (ESI_FTMS, $[M+H]^{1+}$), 533.26474.

[0318] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,5-dimethoxybenzyl)-L-α-glutamine

MS (ESI) *m/z* 477.2; MS (ESI) *m/z* 953.4; HRMS: calcd for $C_{27}H_{28}N_2O_6$ + H+,

477.20201; found (ESI-FTMS, $[M+H]^{1+}$), 477.202.

Example 8DD: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethylbenzyl)-L-α-glutamine

[0319] Step A: *tert*-butyl N^1-(3,4-dimethylbenzyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 543.3; MS (ESI) *m/z* 1085.4; HRMS: calcd for $C_{33}H_{38}N_2O_5$ + H+, 543.28535; found (ESI_FTMS, $[M+H]^{1+}$), 543.28604.

[0320] Step B: *tert*-butyl N^1-(3,4-dimethylbenzyl)-L-α-glutaminate

MS (ESI) *m/z* 321.2; HRMS: calcd for $C_{18}H_{28}N_2O_3$ + H+, 321.21727; found (ESI_FTMS, $[M+H]^{1+}$), 321.21716.

[0321] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethylbenzyl)-L-α-glutaminate

MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.4; HRMS: calcd for $C_{31}H_{36}N_2O_4$ + H+, 501.27478; found (ESI_FTMS, $[M+H]^{1+}$), 501.2735.

[0322] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethylbenzyl)-L-α-glutamine

MS (ESI) *m/z* 445.2; MS (ESI) *m/z* 889.3; HRMS: calcd for $C_{27}H_{28}N_2O_4$ + H+, 445.21218; found (ESI_FTMS, $[M+H]^{1+}$), 445.21199.

Example 8EE: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methylbenzyl)-L-α-glutamine

[0323] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(2-methylbenzyl)-L-α-glutaminate

MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.4; HRMS: calcd for $C_{32}H_{36}N_2O_5$ + H+, 529.26970; found (ESI_FTMS, $[M+H]^{1+}$), 529.27003.

[0324] Step B: *tert*-butyl N^1-(2-methylbenzyl)-L-α-glutaminate

MS (ESI) *m/z* 307.2; MS (ESI) *m/z* 613.4; HRMS: calcd for $C_{17}H_{26}N_2O_3$ + H+, 307.20162; found (ESI_FTMS, $[M+H]^{1+}$), 307.20094.

[0325] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methylbenzyl)-L-α-glutaminate

MS (ESI) *m/z* 487.2; MS (ESI) *m/z* 973.3; HRMS: calcd for $C_{30}H_{34}N_2O_4$ + H+, 487.25913; found (ESI_FTMS, $[M+H]^{1+}$), 487.2588.

[0326] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methylbenzyl)-L-α-glutamine

MS (ESI) *m/z* 431.2; MS (ESI) *m/z* 861.3; HRMS: calcd for $C_{26}H_{26}N_2O_4$ + H+, 431.19653; found (ESI_FTMS, $[M+H]^{1+}$), 431.1966.

Example 8FF: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine

[0327] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(3-phenylpropyl)-L-α-glutaminate

MS (ESI) *m/z* 543.3; HRMS: calcd for $C_{33}H_{38}N_2O_5$ + H+, 543.28535; found (ESI_FTMS, $[M+H]^{1+}$), 543.2847.

[0328] Step B: *tert*-butyl N^1-(3-phenylpropyl)-L-α-glutaminate

MS (ESI) *m/z* 321.2; MS (ESI) *m/z* 641.4; HRMS: calcd for $C_{18}H_{28}N_2O_3$ + H+, 321.21727; found (ESI_FTMS, $[M+H]^{1+}$), 321.2167.

[0329] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutaminate

MS (ESI) *m/z* 501.3; HRMS: calcd for $C_{31}H_{36}N_2O_4$ + H+, 501.27478; found (ESI_FTMS, $[M+H]^{1+}$), 501.2742.

[0330] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine

MS (ESI) *m/z* 445.2; HRMS: calcd for $C_{27}H_{28}N_2O_4$ + H+, 445.21218; found (ESI_FTMS, $[M+H]^{1+}$), 445.2121.

Example 8GG: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-2,3-dihydro-1*H*-inden-2-yl-L-α-glutamine

[0331] Step A: *tert*-butyl N^1-2,3-dihydro-1*H*-inden-2-yl-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 541.2; MS (ESI) *m/z* 1081.4; HRMS: calcd for $C_{33}H_{36}N_2O_5$ + H+, 541.26970; found (ESI-FTMS, $[M+H]^{1+}$), 541.27088.

[0332] Step B: *tert*-butyl N^1-2,3-dihydro-1*H*-inden-2-yl-L-α-glutaminate

MS (ESI) *m/z* 319.1; MS (ESI) *m/z* 637.3; HRMS: calcd for $C_{18}H_{26}N_2O_3$ + H+, 319.20162; found (ESI-FTMS, $[M+H]^{1+}$), 319.20275.

[0333] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-2,3-dihydro-1*H*-inden-2-yl-L-α-glutaminate

MS (ESI) *m/z* 499.2; MS (ESI) *m/z* 997.4; HRMS: calcd for $C_{31}H_{34}N_2O_4$ + H+, 499.25913; found (ESI-FTMS, $[M+H]^{1+}$), 499.258.

[0334] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-2,3-dihydro-1*H*-inden-2-yl-L-α-glutamine

MS (ESI) *m/z* 441.2; MS (ESI) *m/z* 883.3; HRMS: calcd for $C_{27}H_{26}N_2O_4$ + H+, 443.19653; found (ESI-FTMS, $[M+H]^{1+}$), 443.19699.

Example 8HH: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,3-dimethylbenzyl)-L-α-glutamine

[0335] Step A: *tert*-butyl N^1-(2,3-dimethylbenzyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 543.2; MS (ESI) *m/z* 1085.4; HRMS: calcd for $C_{33}H_{38}N_2O_5$ + H+, 543.28535; found (ESI-FTMS, $[M+H]^{1+}$), 543.28623.

[0336] Step B: *tert*-butyl N^1-(2,3-dimethylbenzyl)-L-α-glutaminate

MS (ESI) *m/z* 321.2; MS (ESI) *m/z* 641.4; HRMS: calcd for $C_{18}H_{28}N_2O_3$ + H+, 321.21727; found (ESI-FTMS, $[M+H]^{1+}$), 321.2186.

[0337] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,3-dimethylbenzyl)-L-α-glutaminate

MS (ESI) *m/z* 501.2; MS (ESI) *m/z* 1001.4; HRMS: calcd for $C_{31}H_{36}N_2O_4$ + H+, 501.27478; found (ESI-FTMS, $[M+H]^{1+}$), 501.27629.

[0338] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,3-dimethylbenzyl)-L-α-glutamine

MS (ESI) *m/z* 443.2; HRMS: calcd for $C_{27}H_{28}N_2O_4$ + H+, 445.21218; found (ESI-FTMS, $[M+H]^{1+}$), 445.21354.

Example 8II: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-phenylbutyl)-L-α-glutamine

[0339] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(4-phenylbutyl)-L-α-glutaminate

MS (ESI) *m/z* 557.2; MS (ESI) *m/z* 1113.4; HRMS: calcd for $C_{34}H_{40}N_2O_5$ + H+, 557.30100; found (ESI-FTMS, $[M+H]^{1+}$), 557.30162.

[0340] Step B: *tert*-butyl N^1-(4-phenylbutyl)-L-α-glutaminate

MS (ESI) *m/z* 335.2; HRMS: calcd for $C_{19}H_{30}N_2O_3$ + H+, 335.23292; found (ESI-FTMS, $[M+H]^{1+}$), 335.23453;

[0341] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-phenylbutyl)-L-α-glutaminate

MS (ESI) *m/z* 515.3; MS (ESI) *m/z* 1029.5; HRMS: calcd for $C_{32}H_{38}N_2O_4$ + H+, 515.29043; found (ESI-FTMS, $[M+H]^{1+}$), 515.29152.

[0342] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-phenylbutyl)-L-α-glutamine

MS (ESI) *m/z* 459.2; MS (ESI) *m/z* 917.4; HRMS: calcd for $C_{28}H_{30}N_2O_4$ + H+, 459.22783; found (ESI-FTMS, $[M+H]^{1+}$), 459.22972.

Example 8JJ: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-iodobenzyl)-L-α-glutamine

[0343] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(3-iodobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 641.1; MS (ESI) *m/z* 1281.1; HRMS: calcd for $C_{31}H_{33}IN_2O_5$ + H+, 641.15070; found (ESI-FTMS, $[M+H]^{1+}$), 641.15111.

[0344] Step B: *tert*-butyl N^1-(3-iodobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 419.1; MS (ESI) *m/z* 837.1; HRMS: calcd for $C_{16}H_{23}IN_2O_3$ + H+, 419.08262; found (ESI-FTMS, $[M+H]^{1+}$), 419.08459.

[0345] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-iodobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 599.1; MS (ESI) *m/z* 1197.1; HRMS: calcd for $C_{29}H_{31}IN_2O_4$ + H+, 599.14013; found (ESI-FTMS, $[M+H]^{1+}$), 599.1414.

[0346] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-iodobenzyl)-L-α-glutamine

MS (ESI) *m/z* 543.1; MS (ESI) *m/z* 1085.1; MS (ESI) *m/z* 601.1; HRMS: calcd for $C_{25}H_{23}IN_2O_4$ + H+, 543.07753; found (ESI-FTMS, $[M+H]^{1+}$), 543.07723.

Example 8KK: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-*tert*-butylbenzyl)-L-α-glutamine

[0347] Step A: *tert*-butyl N^1-(4-*tert*-butylbenzyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 571.3; MS (ESI) *m/z* 1141.6; HRMS: calcd for $C_{35}H_{42}N_2O_5$ + H+, 571.31665; found (ESI_FT, $[M+H]^{1+}$), 571.31581.

[0348] Step B: *tert*-butyl N^1-(4-*tert*-butylbenzyl)-L-α-glutaminate

MS (ESI) *m/z* 349.2; HRMS: calcd for $C_{20}H_{32}N_2O_3$ + H+, 349.24857; found (ESI-FTMS, $[M+H]^{1+}$), 349.2489.

[0349] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-*tert*-butylbenzyl)-L-α-glutaminate

MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.4; HRMS: calcd for $C_{33}H_{40}N_2O_4$ + H+, 529.30608; found (ESI-FTMS, $[M+H]^{1+}$), 529.30622.

[0350] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-*tert*-butylbenzyl)-L-α-glutamine

MS (ESI) *m/z* 473.2; MS (ESI) *m/z* 945.3; MS (ESI) *m/z* 531.2; HRMS: calcd for $C_{29}H_{32}N_2O_4$ + H+, 473.24348; found (ESI-FTMS, $[M+H]^{1+}$), 473.24348.

Example 8LL: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-iodobenzyl)-L-α-glutamine

[0351] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(4-iodobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 641.1; MS (ESI) *m/z* 1281.1; HRMS: calcd for $C_{31}H_{33}IN_2O_5$ + H+, 641.15070; found (ESI-FTMS, $[M+H]^{1+}$), 641.15129.

[0352] Step B: *tert*-butyl N^1-(4-iodobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 419; HRMS: calcd for $C_{16}H_{23}IN_2O_3$ + H+, 419.08262; found (ESI-FTMS, $[M+H]^{1+}$), 419.08332.

[0353] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-iodobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 599; MS (ESI) *m/z* 1197; HRMS: calcd for $C_{29}H_{31}IN_2O_4$ + H+, 599.14013; found (ESI-FTMS, $[M+H]^{1+}$), 599.1407.

[0354] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-iodobenzyl)-L-α-glutamine

MS (ESI) *m/z* 543; MS (ESI) *m/z* 1085; HRMS: calcd for $C_{25}H_{23}IN_2O_4$ + H+, 543.07753; found (ESI-FTMS, $[M+H]^{1+}$), 543.07755.

Example 8MM: N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1-dimethylpropyl)-L-α-glutamine

[0355] Step A: *tert*-butyl N^1-(1,1-dimethylpropyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 495.3; HRMS: calcd for $C_{29}H_{38}N_2O_5$ + H+, 495.28535; found (ESI_FT, $[M+H]^{1+}$), 495.28577.

[0356] Step B: *tert*-butyl N^1-(1,1-dimethylpropyl)-L-α-glutaminate

MS (ESI) *m/z* 273.2; HRMS: calcd for $C_{14}H_{28}N_2O_3$ + H+, 273.21727; found (ESI-FTMS, $[M+H]^{1+}$), 273.21738.

[0357] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1-dimethylpropyl)-L-α-glutaminate

MS (ESI) *m/z* 453.2; MS (ESI) *m/z* 905.5; HRMS: calcd for $C_{27}H_{36}N_2O_4$ + H+, 453.27478; found (ESI-FTMS, $[M+H]^{1+}$), 453.27627.

[0358] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1-dimethylpropyl)-L-α-glutamine

MS (ESI) *m/z* 397.2; MS (ESI) *m/z* 793.4; HRMS: calcd for $C_{23}H_{28}N_2O_4$ + H+, 397.21218; found (ESI-FTMS, $[M+H]^{1+}$), 397.2139.

Example 8NN: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0359] Step A: *tert*-butyl N^1-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 591.1; MS (ESI) *m/z* 1181.2; HRMS: calcd for $C_{34}H_{39}ClN_2O_5$ + H+, 591.26203; found (ESI-FTMS, $[M+H]^{1+}$), 591.26263.

[0360] Step B: *tert*-butyl N^1-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutaminate

MS (ESI) *m/z* 369.1; MS (ESI) *m/z* 737.2; HRMS: calcd for $C_{19}H_{29}ClN_2O_3$ + H+, 369.19395; found (ESI-FTMS, $[M+H]^{1+}$), 369.19351.

[0361] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutaminate

MS (ESI) *m/z* 549.1; MS (ESI) *m/z* 1097.2; RMS: calcd for $C_{32}H_{37}ClN_2O_4$ + H+, 549.25146; found (ESI-FTMS, $[M+H]^{1+}$), 549.25189.

[0362] Step D: ^{2}-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine

MS (ESI) *m/z* 493.1; HRMS: calcd for $C_{28}H_{29}ClN_2O_4$ + H+, 493.18886; found (ESI-FTMS, $[M+H]^{1+}$), 493.1895.

Example 8OO: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0363] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutaminate

MS (ESI) *m/z* 575.3; MS (ESI) *m/z* 1149.4; HRMS: calcd for $C_{34}H_{39}FN_2O_5$ + H+, 575.29158; found (ESI-FTMS, $[M+H]^{1+}$), 575.29261.

[0364] Step B: *tert*-butyl N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutaminate

MS (ESI) *m/z* 353.2; HRMS: calcd for $C_{19}H_{29}FN_2O_3$ + H+, 353.22350; found (ESI-FTMS, $[M+H]^{1+}$), 353.22526.

[0365] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutaminate

MS (ESI) *m/z* 533.2; MS (ESI) *m/z* 1065.4; HRMS: calcd for $C_{32}H_{37}FN_2O_4$ + H+, 533.28101; found (ESI-FTMS, $[M+H]^{1+}$), 533.28063.

[0366] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

MS (ESI) *m/z* 477.2; MS (ESI) *m/z* 953.3; HRMS: calcd for $C_{28}H_{29}FN_2O_4$ + H+, 477.21841; found (ESI-FTMS, $[M+H]^{1+}$), 477.21783.

Example 8PP: N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0367] Step A: *tert*-butyl N^1-(1,1-dimethyl-2-phenylethyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 557.2; HRMS: calcd for $C_{34}H_{40}N_2O_5$ + H+, 557.30100; found (ESI-FTMS, $[M+H]^{1+}$), 557.2994.

[0368] Step B: *tert*-butyl N^1-(1,1-dimethyl-2-phenylethyl)-L-α-glutaminate

MS (ESI) *m/z* 335.1; MS (ESI) *m/z* 669.3; HRMS: calcd for $C_{19}H_{30}N_2O_3$ + H+, 335.23292; found (ESI-FTMS, $[M+H]^{1+}$), 335.23259.

[0369] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1-dimethyl-2-phenylethyl)-L-α-glutaminate

MS (ESI) *m/z* 515.2; MS (ESI) *m/z* 1029.3; HRMS: calcd for $C_{32}H_{38}N_2O_4$ + H+, 515.29043; found (ESI-FTMS, $[M+H]^{1+}$), 515.29018.

[0370] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

MS (ESI) *m/z* 459.1; MS (ESI) *m/z* 917.3; HRMS: calcd for $C_{28}H_{30}N_2O_4$ + H+, 459.22783; found (ESI-FTMS, $[M+H]^{1+}$), 459.22858.

Example 8QQ: N^2-(biphenyl-4-ylcarbonyl)-N^1-(3-isopropoxypropyl)-L-α-glutamine

[0371] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(3-isopropoxypropyl)-L-α-glutaminate

MS (ESI) *m/z* 525.3; MS (ESI) *m/z* 1049.5; HRMS: calcd for $C_{30}H_{40}N_2O_6$ + H+, 525.29591; found (ESI-FTMS, $[M+H]^{1+}$), 525.29528.

[0372] Step B: *tert*-butyl N^1-(3-isopropoxypropyl)-L-α-glutaminate

MS (ESI) *m/z* 303.2; HRMS: calcd for $C_{15}H_{30}N_2O_4$ + H+, 303.22783; found (ESI-FTMS, $[M+H]^{1+}$), 303.22747.

[0373] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(3-isopropoxypropyl)-L-α-glutaminate

MS (ESI) *m/z* 483.3; MS (ESI) *m/z* 965.5; HRMS: calcd for $C_{28}H_{38}N_2O_5$ + H+, 483.28535; found (ESI-FTMS, $[M+H]^{1+}$), 483.28364.

[0374] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(3-isopropoxypropyl)-L-α-glutamine

MS (ESI) *m/z* 427.2; MS (ESI) *m/z* 853.4; MS (ESI) *m/z* 449.2; HRMS: calcd for $C_{24}H_{30}N_2O_5$ + H+, 427.22275; found (ESI-FTMS, $[M+H]^{1+}$), 427.22227.

Example 8RR: N^2-(biphenyl-4-ylcarbonyl)-N^1-(3-methylbutyl)-L-α-glutamine

[0375] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(3-methylbutyl)-L-α-glutaminate

MS (ESI) *m/z* 495.2; MS (ESI) *m/z* 989.5; HRMS: calcd for $C_{29}H_{38}N_2O_5$ + H+, 495.28535; found (ESI-FTMS, $[M+H]^{1+}$), 495.28729.

[0376] Step B: *tert*-butyl N^1-(3-methylbutyl)-L-α-glutaminate

MS (ESI) *m/z* 273.2; HRMS: calcd for $C_{14}H_{28}N_2O_3$ + H+, 273.21727; found (ESI-FTMS, $[M+H]^{1+}$), 273.21718.

[0377] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(3-methylbutyl)-L-α-glutaminate

MS (ESI) *m/z* 453.3; MS (ESI) *m/z* 905.5; MS (ESI) *m/z* 475.2; HRMS: calcd for $C_{27}H_{36}N_2O_4$ + H+, 453.27478; found (ESI-FTMS, $[M+H]^{1+}$), 453.27427.

[0378] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(3-methylbutyl)-L-α-glutamine

MS (ESI) *m/z* 397.2; MS (ESI) *m/z* 793.3; HRMS: calcd for $C_{23}H_{28}N_2O_4$ + H+, 397.21218; found (ESI-FTMS, $[M+H]^{1+}$), 397.21129.

Example 8SS: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)ethyl]-L-α-glutamine

[0379] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[2-(4-fluorophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 547.2; MS (ESI) *m/z* 1093.3; HRMS: calcd for $C_{32}H_{35}FN_2O_5$ + H+, 547.26028; found (ESI-FTMS, $[M+H]^{1+}$), 547.26067.

[0380] Step B: *tert*-butyl N^1-[2-(4-fluorophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 325.1; HRMS: calcd for $C_{17}H_{25}FN_2O_3$ + H+, 325.19220; found (ESI-FTMS, $[M+H]^{1+}$), 325.19212.

[0381] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 505.2; MS (ESI) *m/z* 1009.3; HRMS: calcd for $C_{30}H_{33}FN_2O_4$ + H+, 505.24971; found (ESI-FTMS, $[M+H]^{1+}$), 505.25021.

[0382] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 449.1; MS (ESI) *m/z* 897.2; HRMS: calcd for $C_{26}H_{25}FN_2O_4$ + H+, 449.18711; found (ESI-FTMS, $[M+H]^{1+}$), 449.18705.

Example 8TT: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-fluorophenyl)ethyl]-L-α-glutamine

[0383] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[2-(2-fluorophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 547.2; MS (ESI) *m/z* 1093.3; HRMS: calcd for $C_{32}H_{35}FN_2O_5$ + H+, 547.26028; found (ESI-FTMS, $[M+H]^{1+}$), 547.26138.

[0384] Step B: *tert*-butyl N^1-[2-(2-fluorophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 325.1; MS (ESI) *m/z* 649.3; HRMS: calcd for $C_{17}H_{25}FN_2O_3$ + H+, 325.19220; found (ESI-FTMS, $[M+H]^{1+}$), 325.19217.

[0385] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-fluorophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 505.2; MS (ESI) *m/z* 1009.3; HRMS: calcd for $C_{30}H_{33}FN_2O_4$ + H+, 505.24971; found (ESI-FTMS, $[M+H]^{1+}$), 505.2497.

[0386] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-fluorophenyl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 449.1; MS (ESI) *m/z* 897.2; HRMS: calcd for $C_{26}H_{25}FN_2O_4$ + H+, 449.18711; found (ESI-FTMS, $[M+H]^{1+}$), 449.18744.

Example 8UU: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-chlorophenyl)ethyl]-L-α-glutamine

[0387] Step A: *tert*-butyl N^1-[2-(4-chlorophenyl)ethyl]-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 563.1; MS (ESI) *m/z* 1125.2; HRMS: calcd for $C_{32}H_{35}ClN_2O_5$ + Na+, 585.21267; found (ESI-FTMS, $[M+Na]^{1+}$), 585.21454.

[0388] Step B: *tert*-butyl N^1-[2-(4-chlorophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 341.1; MS (ESI) *m/z* 681.2; HRMS: calcd for $C_{17}H_{25}ClN_2O_3$ + H+, 341.16265; found (ESI-FTMS, $[M+H]^{1+}$), 341.16311.

[0389] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-chlorophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 521.2; MS (ESI) *m/z* 1041.3; HRMS: calcd for $C_{30}H_{33}ClN_2O_4$ + Na+, 543.20210; found (ESI-FTMS, $[M+Na]^{1+}$), 543.20393.

[0390] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-chlorophenyl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 463.1; MS (ESI) *m/z* 927.1; HRMS: calcd for $C_{26}H_{25}ClN_2O_4$ + H+,

465.15756; found (ESI-FTMS, $[M+H]^{1+}$), 465.15776.

Example 8VV: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-chlorophenyl)ethyl]-L-α-glutamine

[0391] Step A: *tert*-butyl N^1-[2-(2-chlorophenyl)ethyl]-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 563.1; MS (ESI) *m/z* 1125.2; HRMS: calcd for $C_{32}H_{35}ClN_2O_5$ + H+, 563.23073; found (ESI-FTMS, $[M+H]^{1+}$), 563.23042.

[0392] Step B: *tert*-butyl N^1-[2-(2-chlorophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 341.2; MS (ESI) *m/z* 681.3; MS (ESI) *m/z* 703.3; HRMS: calcd for $C_{17}H_{25}ClN_2O_3$ + H+, 341.16265; found (ESI-FTMS, $[M+H]^{1+}$), 341.16301.

[0393] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-chlorophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 521.2; MS (ESI) *m/z* 1041.4; HRMS: calcd for $C_{30}H_{33}ClN_2O_4$ + H+, 521.22016; found (ESI-FTMS, $[M+H]^{1+}$), 521.22075.

[0394] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-chlorophenyl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 465; MS (ESI) *m/z* 487; HRMS: calcd for $C_{26}H_{25}ClN_2O_4$ + H+, 465.15756; found (ESI-FTMS, $[M+H]^{1+}$), 465.15834.

Example 8WW: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-thienyl)ethyl]-L-α-glutamine

[0395] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[2-(2-thienyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 535.1; MS (ESI) *m/z* 1069.2; HRMS: calcd for $C_{30}H_{34}N_2O_5S$ + H+, 535.22612; found (ESI-FTMS, $[M+H]^{1+}$), 535.22756.

[0396] Step B: *tert*-butyl N^1-[2-(2-thienyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 313.1; MS (ESI) *m/z* 625.2; HRMS: calcd for $C_{15}H_{24}N_2O_3S$ + H+, 313.15804; found (ESI-FTMS, $[M+H]^{1+}$), 313.15788.

[0397] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-thienyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 493.2; MS (ESI) *m/z* 985.4; HRMS: calcd for $C_{28}H_{32}N_2O_4S$ + H+, 493.21555; found (ESI-FTMS, $[M+H]^{1+}$), 493.21561.

[0398] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-thienyl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 437.1; MS (ESI) *m/z* 873.3; HRMS: calcd for $C_{24}H_{24}N_2O_4S$ + H+, 437.15295; found (ESI-FTMS, $[M+H]^{1+}$), 437.15163.

Example 8XX: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-fluorobenzyl)-L-α-glutamine

[0399] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(3-fluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 533.2; HRMS: calcd for $C_{31}H_{33}FN_2O_5$ + H+, 533.24463; found (ESI_FTMS, $[M+H]^{1+}$), 533.2447.

[0400] Step B: *tert*-butyl N^1-(3-fluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 311.2; HRMS: calcd for $C_{16}H_{23}FN_2O_3$ + H+, 311.17655; found (ESI_FTMS, $[M+H]^{1+}$), 311.1764.

[0401] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-fluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 491.2; MS (ESI) *m/z* 981.4; HRMS: calcd for $C_{29}H_{31}FN_2O_4$ + H+, 491.23406; found (ESI_FTMS, $[M+H]^{1+}$), 491.2339.

[0402] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-fluorobenzyl)-L-α-glutamine

MS (ESI) *m/z* 435.1; MS (ESI) *m/z* 869.2; HRMS: calcd for $C_{25}H_{23}FN_2O_4$ + H+, 435.17146; found (ESI_FTMS, $[M+H]^{1+}$), 435.1712.

Example 8YY: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3-chlorophenyl)ethyl]-L-α-glutamine

[0403] Step A: *tert*-butyl N^1-[2-(3-chlorophenyl)ethyl]-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS *m/z* 03-305496LMS; HRMS: calcd for $C_{32}H_{35}ClN_2O_5$ + H+, 563.23073; found (ESI_FTMS, $[M+H]^{1+}$), 563.2309.

[0404] Step B: *tert*-butyl N^1-[2-(3-chlorophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 341.1; HRMS: calcd for $C_{17}H_{25}ClN_2O_3$ + H+, 341.16265; found (ESI_FTMS, $[M+H]^{1+}$), 341.1611.

[0405] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3-chlorophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 521.1; MS (ESI) *m/z* 1041.1; HRMS: calcd for $C_{30}H_{33}ClN_2O_4$ + H+, 521.22016; found (ESI-FTMS, $[M+H]^{1+}$), 521.22136.

[0406] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3-chlorophenyl)ethyl]-L-α-glutamine

MS (ESI-) *m/z* 463.2; MS (ESI-) *m/z* 197; HRMS: calcd for $C_{26}H_{25}ClN_2O_4$ + H+, 465.15756; found (ESI-FTMS, $[M+H]^{1+}$), 465.15709.

Example 8ZZ: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-fluorobenzyl)-L-α-glutamine

[0407] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(2-fluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 533.1; MS (ESI) *m/z* 1065.1; HRMS: calcd for $C_{31}H_{33}FN_2O_5$ + H+, 533.24463; found (ESI_FTMS, $[M+H]^{1+}$), 533.24461.

[0408] Step B: *tert*-butyl N^1-(2-fluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 311.1; MS (ESI) *m/z* 621.2; HRMS: calcd for $C_{16}H_{23}FN_2O_3$ + H+, 311.17655; found (ESI_FTMS, $[M+H]^{1+}$), 311.1762.

[0409] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-fluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 491.1; MS (ESI) *m/z* 981.2; HRMS: calcd for $C_{29}H_{31}FN_2O_4$ + H+, 491.23406; found (ESI-FTMS, $[M+H]^{1+}$), 491.23526.

[0410] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-fluorobenzyl)-L-α-glutamine

MS (ESI-) *m/z* 433.1; HRMS: calcd for $C_{25}H_{23}FN_2O_4$ + H+, 435.17146; found (ESI-FTMS, $[M+H]^{1+}$), 435.17161.

Example 8AAA: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-difluorobenzyl)-L-α-glutamine

[0411] Step A: *tert*-butyl N^1-(3,4-difluorobenzyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 551.2; MS (ESI) *m/z* 1101.4; HRMS: calcd for $C_{31}H_{32}F_2N_2O_5$ + H+, 551.23521; found (ESI_FT, $[M+H]^{1+}$), 551.23407.

[0412] Step B: *tert*-butyl N^1-(3,4-difluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 329; MS (ESI) *m/z* 657.2; HRMS: calcd for $C_{16}H_{22}F_2N_2O_3$ + H+, 329.16712; found (ESI_FTMS, $[M+H]^{1+}$), 329.1664.

[0413] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-difluorobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 509.1; MS (ESI) *m/z* 1017.1; HRMS: calcd for $C_{29}H_{30}F_2N_2O_4$ + H+, 509.22464; found (ESI-FTMS, $[M+H]^{1+}$), 509.22485.

[0414] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-difluorobenzyl)-L-α-glutamine

MS (ESI-) *m/z* 451.1; HRMS: calcd for $C_{25}H_{22}F_2N_2O_4$ + H+, 453.16204; found (ESI-FTMS, $[M+H]^{1+}$), 453.1614.

Example 8BBB: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(sec-butyl)-L-α-glutamine

[0415] Step A: *tert*-butyl N^1-(sec-butyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 481.2; HRMS: calcd for $C_{28}H_{36}N_2O_5$ + H+, 481.26970; found (ESI-FTMS, $[M+H]^{1+}$), 481.26966.

[0416] Step B: *tert*-butyl N^1-(sec-butyl)-L-α-glutaminate

MS (ESI) *m/z* 259.1; HRMS: calcd for $C_{13}H_{26}N_2O_3$ + H+, 259.20162; found (ESI-FTMS, $[M+H]^{1+}$), 259.20164.

[0417] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(sec-butyl)-L-α-glutaminate

MS (ESI) *m/z* 439.2; MS (ESI) *m/z* 877.4; HRMS: calcd for $C_{26}H_{34}N_2O_4$ + H+, 439.25913; found (ESI-FTMS, $[M+H]^{1+}$), 439.25972.

[0418] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(sec-butyl)-L-α-glutamine

MS (ESI) *m/z* 383.1; MS (ESI) *m/z* 765.3; MS (ESI) *m/z* 441.2; HRMS: calcd for $C_{22}H_{26}N_2O_4$ + H+, 383.19653; found (ESI-FTMS, $[M+H]^{1+}$), 383.19745.

Example 8CCC: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(cyclopropylmethyl)-L-α-glutamine

[0419] Step A: *tert*-butyl N^1-(cyclopropylmethyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 479.2; MS (ESI) *m/z* 957.3; HRMS: calcd for $C_{28}H_{34}N_2O_5$ + H+, 479.25405; found (ESI-FTMS, $[M+H]^{1+}$), 479.25563.

[0420] Step B: *tert*-butyl N^1-(cyclopropylmethyl)-L-α-glutaminate

MS (ESI) *m/z* 257.1; HRMS: calcd for $C_{13}H_{24}N_2O_3$ + H+, 257.18597; found (ESI-FTMS, $[M+H]^{1+}$), 257.18608.

[0421] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(cyclopropylmethyl)-L-α-glutaminate

MS (ESI) *m/z* 437.2; MS (ESI) *m/z* 873.3; HRMS: calcd for $C_{26}H_{32}N_2O_4$ + H+, 437.24348; found (ESI-FTMS, $[M+H]^{1+}$), 437.24446.

[0422] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(cyclopropylmethyl)-L-α-glutamine

MS (ESI) *m/z* 381.1; MS (ESI) *m/z* 761.2; HRMS: calcd for $C_{22}H_{24}N_2O_4$ + H+, 381.18088; found (ESI-FTMS, $[M+H]^{1+}$), 381.18186.

Example 8DDD: N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-morpholin-4-ylethyl)-L-α-glutamine

[0423] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(2-morpholin-4-ylethyl)-L-α-glutaminate

MS (ESI) *m/z* 538.3; HRMS: calcd for $C_{30}H_{39}N_3O_6$ + H+, 538.29116; found (ESI-FTMS, $[M+H]^{1+}$), 538.29233.

[0424] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-morpholin-4-ylethyl)-L-α-glutaminate

MS (ESI) *m/z* 496.2; HRMS: calcd for $C_{28}H_{37}N_3O_5$ + H+, 496.28060; found (ESI-FTMS, $[M+H]^{1+}$), 496.28079.

[0425] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-morpholin-4-ylethyl)-L-α-glutamine

MS (ESI) *m/z* 440.2; HRMS: calcd for $C_{24}H_{29}N_3O_5$ + H+, 440.21800; found (ESI-FTMS, $[M+H]^{1+}$), 440.21827.

Example 8EEE: N^2-(biphenyl-4-ylcarbonyl)-N^1,N^1-diethyl-L-α-glutamine

[0426] Step A: *tert*-butyl N^1,N^1-diethyl-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 481.3; MS (ESI) *m/z* 961.5; HRMS: calcd for $C_{28}H_{36}N_2O_5$ + Na+, 503.25164; found (ESI-FTMS, $[M+Na]^{1+}$), 503.25163.

[0427] Step B: *tert*-butyl N^1,N^1-diethyl-L-α-glutaminate

MS (ESI) *m/z* 259.2; HRMS: calcd for $C_{13}H_{26}N_2O_3$ + H+, 259.20162; found (ESI-FTMS, $[M+H]^{1+}$), 259.20149.

[0428] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1,N^1-diethyl-L-α-glutaminate

MS (ESI) *m/z* 439.2; MS (ESI) *m/z* 877.4; HRMS: calcd for $C_{26}H_{34}N_2O_4$ + H+, 439.25913; found (ESI-FTMS, $[M+H]^{1+}$), 439.26093.

[0429] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1,N^1-diethyl-L-α-glutamine

MS (ESI) *m/z* 383.2; MS (ESI) *m/z* 765.4; HRMS: calcd for $C_{22}H_{26}N_2O_4$ + H+, 383.19653; found (ESI-FTMS, $[M+H]^{1+}$), 383.19675.

Example 8FFF: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-phenylethyl)-L-α-glutamine

[0430] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(2-phenylethyl)-L-α-glutaminate

MS (ESI) *m/z* 529.2; HRMS: calcd for $C_{32}H_{36}N_2O_5$ + H+, 529.26970; found (ESI_FTMS, $[M+H]^{1+}$), 529.2693.

[0431] Step B: *tert*-butyl N^1-(2-phenylethyl)-L-α-glutaminate

HRMS: calcd for $C_{17}H_{26}N_2O_3$ + H+, 307.20162; found (ESI_FTMS, $[M+H]^{1+}$), 307.2011.

[0432] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-phenylethyl)-L-α-glutaminate

MS (ESI) *m/z* 487.2; MS (ESI) *m/z* 973.3; HRMS: calcd for $C_{30}H_{34}N_2O_4$ + H+, 487.25913; found (ESI_FTMS, $[M+H]^{1+}$), 487.2588.

[0433] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-phenylethyl)-L-α-glutamine

MS (ESI) *m/z* 431.2; MS (ESI) *m/z* 861.3; HRMS: calcd for $C_{26}H_{26}N_2O_4$ + H+, 431.19653; found (ESI_FTMS, $[M+H]^{1+}$), 431.1963.

Example 8GGG: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[3-(trifluoromethyl)benzyl]-L-α-glutamine

[0434] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[3-(trifluoromethyl)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 583.2; HRMS: calcd for $C_{32}H_{33}F_3N_2O_5$ + H+, 583.24143; found (ESI_FTMS, $[M+H]^{1+}$), 583.2409.

[0435] Step B: *tert*-butyl N^1-[3-(trifluoromethyl)benzyl]-L-α-glutaminate

HRMS: calcd for $C_{17}H_{23}F_3N_2O_3$ + H+, 361.17335; found (ESI_FTMS, $[M+H]^{1+}$), 361.173.

[0436] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[3-(trifluoromethyl)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 541.2; MS (ESI) *m/z* 1081.3; HRMS: calcd for $C_{30}H_{31}F_3N_2O_4$ + H+, 541.23087; found (ESI_FTMS, $[M+H]^{1+}$), 541.2301.

[0437] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[3-(trifluoromethyl)benzyl]-L-α-glutamine

MS (ESI) *m/z* 485.2; MS (ESI) *m/z* 969.3; HRMS: calcd for $C_{26}H_{23}F_3N_2O_4$ + H+, 485.16827; found (ESI_FTMS, $[M+H]^{1+}$), 485.1682.

Example 8HHH: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(trifluoromethyl)benzyl]-L-α-glutamine

[0438] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[2-(trifluoromethyl)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 583.2; HRMS: calcd for $C_{32}H_{33}F_3N_2O_5$ + H+, 583.24143; found (ESI_FT, $[M+H]^{1+}$), 583.24162.

[0439] Step B: *tert*-butyl N^1-[2-(trifluoromethyl)benzyl]-L-α-glutaminate

HRMS: calcd for $C_{17}H_{23}F_3N_2O_3$ + H+, 361.17335; found (ESI_FTMS, $[M+H]^{1+}$), 361.1725.

[0440] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(trifluoromethyl)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 541.2; MS (ESI) *m/z* 1081.2; HRMS: calcd for $C_{30}H_{31}F_3N_2O_4$ + H+, 541.23087; found (ESI_FTMS, $[M+H]^{1+}$), 541.23091.

[0441] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(trifluoromethyl)benzyl]-L-α-glutamine

MS (ESI) *m/z* 485; MS (ESI) *m/z* 969; HRMS: calcd for $C_{26}H_{23}F_3N_2O_4$ + H+, 485.16827; found (ESI_FTMS, $[M+H]^{1+}$), 485.168.

Example 8III: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methylbenzyl)-L-α-glutamine

[0442] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(4-methylbenzyl)-L-α-glutaminate

MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.4; HRMS: calcd for $C_{32}H_{36}N_2O_5$ + H+, 529.26970; found (ESI_FT, $[M+H]^{1+}$), 529.26796.

[0443] Step B: *tert*-butyl N^1-(4-methylbenzyl)-L-α-glutaminate

HRMS: calcd for $C_{17}H_{26}N_2O_3$ + H+, 307.20162; found (ESI-FTMS, $[M+H]^{1+}$), 307.20274.

[0444] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methylbenzyl)-L-α-glutaminate

HRMS: calcd for $C_{30}H_{34}N_2O_4$ + H+, 487.25913; found (ESI-FTMS, $[M+H]^{1+}$), 487.25856.

[0445] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methylbenzyl)-L-α-glutamine

HRMS: calcd for $C_{26}H_{26}N_2O_4$ + H+, 431.19653; found (ESI-FTMS, $[M+H]^{1+}$), 431.19627.

Example 8JJJ: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-heptyl-L-α-glutamine

[0446] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-heptyl-L-α-glutaminate

MS (ESI) *m/z* 523.3; MS (ESI) *m/z* 1045.5; HRMS: calcd for $C_{31}H_{42}N_2O_5$ + H+, 523.31665; found (ESI-FTMS, $[M+H]^{1+}$), 523.31783.

[0447] Step B: *tert*-butyl N^1-heptyl-L-α-glutaminate

HRMS: calcd for $C_{16}H_{32}N_2O_3$ + H+, 301.24857; found (ESI-FTMS, $[M+H]^{1+}$), 301.2499.

[0448] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-heptyl-L-α-glutaminate

HRMS: calcd for $C_{29}H_{40}N_2O_4$ + H+, 481.30608; found (ESI-FTMS, $[M+H]^{1+}$), 481.30706.

[0449] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-heptyl-L-α-glutamine

HRMS: calcd for $C_{25}H_{32}N_2O_4$ + H+, 425.24348; found (ESI-FTMS, $[M+H]^{1+}$), 425.24417.

Example 8KKK: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-bromophenyl)ethyl]-L-α-glutamine

[0450] Step A: *tert*-butyl N^1-[2-(4-bromophenyl)ethyl]-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 607.1; HRMS: calcd for $C_{32}H_{35}BrN_2O_5$ + H+, 607.18021; found (ESI-FTMS, $[M+H]^{1+}$), 607.18182.

[0451] Step B: *tert*-butyl N^1-[2-(4-bromophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 385; HRMS: calcd for $C_{17}H_{25}BrN_2O_3$ + H+, 385.11213; found (ESI-FTMS, $[M+H]^{1+}$), 385.11309.

[0452] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-bromophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 565.1; MS (ESI) *m/z* 1129.1; HRMS: calcd for $C_{30}H_{33}BrN_2O_4$ + H+, 565.16965; found (ESI-FTMS, $[M+H]^{1+}$), 565.17.

[0453] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-bromophenyl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 507.2; HRMS: calcd for $C_{26}H_{25}BrN_2O_4$ + H+, 509.10705; found (ESI-FTMS, $[M+H]^{1+}$), 509.10906.

Example 8LLL: N^2-(biphenyl-4-ylcarbonyl)-N^1-(3,3-dimethylbutyl)-L-α-glutamine

[0454] Step A: *tert*-butyl N^1-(3,3-dimethylbutyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 509.3; MS (ESI) *m/z* 1017.5; HRMS: calcd for $C_{30}H_{40}N_2O_5$ + H+, 509.30100; found (ESI-FTMS, $[M+H]^{1+}$), 509.30165.

[0455] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(3,3-dimethylbutyl)-L-α-glutaminate

MS (ESI) *m/z* 467.3; MS (ESI) *m/z* 933.5; MS (ESI) *m/z* 489.3; HRMS: calcd for $C_{28}H_{38}N_2O_4$ + H+, 467.29043; found (ESI-FTMS, $[M+H]^{1+}$), 467.29134.

[0456] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(3,3-dimethylbutyl)-L-α-glutamine HRMS: calcd for $C_{24}H_{30}N_2O_4$ + H+, 411.22783; found (ESI-FTMS, $[M+H]^{1+}$), 411.22929.

Example 8MMM: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(3-bromophenyl)ethyl]-L-α-glutamine

[0457] Step A: *tert*-butyl N^1-[2-(3-bromophenyl)ethyl]-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 607.1; MS (ESI) *m/z* 1213.3; HRMS: calcd for $C_{32}H_{35}BrN_2O_5$ + H+, 607.18021; found (ESI-FTMS, $[M+H]^{1+}$), 607.18017.

[0458] Step B: *tert*-butyl N^1-[2-(3-bromophenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 385.1; MS (ESI) *m/z* 769.2; HRMS: calcd for $C_{17}H_{25}BrN_2O_3$ + H+, 385.11213; found (ESI-FTMS, $[M+H]^{1+}$), 385.11175.

[0459] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(3-bromophenyl)ethyl]-L-α-glutaminate

HRMS: calcd for $C_{30}H_{33}BrN_2O_4$ + H+, 565.16965; found (ESI-FTMS, $[M+H]^{1+}$), 565.16854.

[0460] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(3-bromophenyl)ethyl]-L-α-glutamine

HRMS: calcd for $C_{26}H_{25}BrN_2O_4$ + H+, 509.10705; found (ESI-FTMS, $[M+H]^{1+}$), 509.10648.

Example 8NNN: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-fluoro-3-(trifluoromethyl)benzyl]-L-α-glutamine

[0461] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[4-fluoro-3-(trifluoromethyl)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 601.2; MS (ESI) *m/z* 1201.3; HRMS: calcd for $C_{32}H_{32}F_4N_2O_5$ + H+, 601.23201; found (ESI-FTMS, $[M+H]^{1+}$), 601.23172.

[0462] Step B: *tert*-butyl N^1-[4-fluoro-3-(trifluoromethyl)benzyl]-L-α-glutaminate

HRMS: calcd for $C_{17}H_{22}F_4N_2O_3$ + H+, 379.16393; found (ESI-FTMS, $[M+H]^{1+}$), 379.16566.

[0463] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-fluoro-3-(trifluoromethyl)benzyl]-L-α-glutaminate

HRMS: calcd for $C_{30}H_{30}F_4N_2O_4$ + H+, 559.22145; found (ESI-FTMS, $[M+H]^{1+}$), 559.22077.

[0464] Step D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-fluoro-3-(trifluoromethyl)benzyl]-L-α-glutamine

HRMS: calcd for $C_{26}H_{22}F_4N_2O_4$ + H+, 503.15885; found (ESI-FTMS, $[M+H]^{1+}$), 503.1582.

Example 8OOO: N^2-(biphenyl-4-ylcarbonyl)-N^1-(3,3-diphenylpropyl)-L-α-glutamine

[0465] Step A: *tert*-butyl N^1-(3,3-diphenylpropyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 619.3; MS (ESI) *m/z* 1237.6; HRMS: calcd for $C_{39}H_{42}N_2O_5$ + H+, 619.31665; found (ESI-FTMS, $[M+H]^{1+}$), 619.31658.

[0466] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(3,3-diphenylpropyl)-L-α-glutaminate

HRMS: calcd for $C_{37}H_{40}N_2O_4$ + H+, 577.30608; found (ESI-FTMS, $[M+H]^{1+}$), 577.30483.

[0467] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(3,3-diphenylpropyl)-L-α-glutamine

HRMS: calcd for $C_{33}H_{32}N_2O_4$ + H+, 521.24348; found (ESI-FTMS, $[M+H]^{1+}$), 521.24166.

Example 8PPP: N^2-(biphenyl-4-ylcarbonyl)-N^1-isopropyl-L-α-glutamine

[0468] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-isopropyl-L-α-glutaminate

MS (ESI) *m/z* 467.2; MS (ESI) *m/z* 933.5; HRMS: calcd for $C_{27}H_{34}N_2O_5$ + Na+, 489.23599; found (ESI-FTMS, $[M+Na]^{1+}$), 489.23577.

[0469] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-isopropyl-L-α-glutaminate

MS (ESI) *m/z* 425.2; MS (ESI) *m/z* 447.2; MS (ESI) *m/z* 871.4; HRMS: calcd for $C_{25}H_{32}N_2O_4$ + Na+, 447.22543; found (ESI-FTMS, $[M+Na]^{1+}$), 447.22701.

[0470] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-isopropyl-L-α-glutamine

MS (ESI) *m/z* 367.2; MS (ESI) *m/z* 735.3; MS (ESI) *m/z* 481.2; HRMS: calcd for $C_{21}H_{24}N_2O_4$ + Na+, 391.16283; found (ESI-FTMS, $[M+Na]^{1+}$), 391.16451.

Example 8QQQ: N^2-(biphenyl-4-ylcarbonyl)-N^1-(pyridin-4-ylmethyl)-L-α-glutamine

[0471] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(pyridin-4-ylmethyl)-L-α-glutaminate

MS (ESI) *m/z* 516.3; HRMS: calcd for $C_{30}H_{33}N_3O_5$ + H+, 516.24930; found (ESI_FTMS, $[M+H]^{1+}$), 516.24875.

[0472] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(pyridin-4-ylmethyl)-L-α-glutaminate

MS (ESI) *m/z* 474.2; HRMS: calcd for $C_{28}H_{31}N_3O_4$ + H+, 474.23873; found (ESI-FTMS, $[M+H]^{1+}$), 474.24265.

[0473] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(pyridin-4-ylmethyl)-L-α-glutamine

HRMS: calcd for $C_{24}H_{23}N_3O_4$ + H+, 418.17613; found (ESI-FTMS, $[M+H]^{1+}$), 418.17812.

Example 8RRR: N^2-(biphenyl-4-ylcarbonyl)-N^1-pentyl-L-α-glutamine

[0474] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-pentyl-L-α-glutaminate

MS (ESI) *m/z* 495.2; MS (ESI) *m/z* 989.5; HRMS: calcd for $C_{29}H_{38}N_2O_5$ + Na+, 517.26729; found (ESI-FTMS, $[M+Na]^{1+}$), 517.26785.

[0475] Step B: *tert*-butyl N^1-pentyl-L-α-glutaminate

MS (ESI) *m/z* 273.2; HRMS: calcd for $C_{14}H_{28}N_2O_3$ + H+, 273.21727; found (ESI-FTMS, $[M+H]^{1+}$), 273.21761.

[0476] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-pentyl-L-α-glutaminate

MS (ESI) *m/z* 453.2; MS (ESI) *m/z* 905.5; HRMS: calcd for $C_{27}H_{36}N_2O_4$ + H+, 453.27478; found (ESI-FTMS, $[M+H]^{1+}$), 453.27694.

[0477] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-pentyl-L-α-glutamine

MS (ESI) *m/z* 397.2; MS (ESI) *m/z* 793.4; HRMS: calcd for $C_{23}H_{28}N_2O_4$ + H+, 397.21218; found (ESI-FTMS, $[M+H]^{1+}$), 397.2136.

Example 8SSS: N^2-(biphenyl-4-ylcarbonyl)-N^1-(*tert*-butyl)-L-α-glutamine

[0478] Step A: *tert*-butyl N^1-(*tert*-butyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 481.2; MS (ESI) *m/z* 961.5; HRMS: calcd for $C_{28}H_{36}N_2O_5$ + H+, 481.26970; found (ESI-FTMS, $[M+H]^{1+}$), 481.27074.

[0479] Step B: *tert*-butyl N^1-(*tert*-butyl)-L-α-glutaminate

MS (ESI) *m/z* 259.1; MS (ESI) *m/z* 517.3; HRMS: calcd for $C_{13}H_{26}N_2O_3$ + H+, 259.20162; found (ESI-FTMS, $[M+H]^{1+}$), 259.20174.

[0480] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(*tert*-butyl)-L-α-glutaminate

MS (ESI) *m/z* 439.2; MS (ESI) *m/z* 877.4; HRMS: calcd for $C_{26}H_{34}N_2O_4$ + H+, 439.25913; found (ESI-FTMS, $[M+H]^{1+}$), 439.25922.

[0481] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(*tert*-butyl)-L-α-glutamine

MS (ESI) *m/z* 383.2; MS (ESI) *m/z* 765.3; HRMS: calcd for $C_{22}H_{26}N_2O_4$ + H+, 383.19653; found (ESI-FTMS, $[M+H]^{1+}$), 383.19812.

Example 8TTT: N^2-(biphenyl-4-ylcarbonyl)-N^1-(1-methyl-1-phenylethyl)-L-α-glutamine

[0482] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(1-methyl-1-phenylethyl)-L-α-glutaminate

MS (ESI) *m/z* 543.2; MS (ESI) *m/z* 1085.4; HRMS: calcd for $C_{33}H_{38}N_2O_5$ + H+, 543.28535; found (ESI-FTMS, $[M+H]^{1+}$), 543.28707.

[0483] Step B: *tert*-butyl N^1-(1-methyl-1-phenylethyl)-L-α-glutaminate

MS (ESI) *m/z* 321.1; MS (ESI) *m/z* 641.3; HRMS: calcd for $C_{18}H_{28}N_2O_3$ + H+, 321.21727; found (ESI-FTMS, $[M+H]^{1+}$), 321.21716.

[0484] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(1-methyl-1-phenylethyl)-L-α-glutaminate

MS (ESI) *m/z* 501.2; MS (ESI) *m/z* 1001.4; HRMS: calcd for $C_{31}H_{36}N_2O_4$ + H+, 501.27478; found (ESI-FTMS, $[M+H]^{1+}$), 501.27462.

[0485] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(1-methyl-1-phenylethyl)-L-α-glutamine

HRMS: calcd for $C_{27}H_{28}N_2O_4$ + H+, 445.21218; found (ESI-FTMS, $[M+H]^{1+}$), 445.21311.

Example 8UUU: N^2-(biphenyl-4-ylcarbonyl)-N^1-(2,2-dimethylpropyl)-L-α-glutamine

[0486] Step A: *tert*-butyl N^1-(2,2-dimethylpropyl)-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 495.2; MS (ESI) *m/z* 989.4; HRMS: calcd for $C_{29}H_{38}N_2O_5$ + H+, 495.28535; found (ESI-FTMS, $[M+H]^{1+}$), 495.2859.

[0487] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(2,2-dimethylpropyl)-L-α-glutaminate

MS (ESI) *m/z* 453.2; MS (ESI) *m/z* 905.4; HRMS: calcd for $C_{27}H_{36}N_2O_4$ + H+, 453.27478; found (ESI-FTMS, $[M+H]^{1+}$), 453.2764.

[0488] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(2,2-dimethylpropyl)-L-α-glutamine

MS (ESI) *m/z* 397.1; MS (ESI) *m/z* 793.3; HRMS: calcd for $C_{23}H_{28}N_2O_4$ + H+, 397.21218; found (ESI-FTMS, $[M+H]^{1+}$), 397.21242.

Example 8VVV: N^2-(biphenyl-4-ylcarbonyl)-N^1-hexyl-L-α-glutamine

[0489] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-hexyl-L-α-glutaminate

MS (ESI) *m/z* 509.3; MS (ESI) *m/z* 1017.5; HRMS: calcd for $C_{30}H_{40}N_2O_5$ + H+, 509.30100; found (ESI-FTMS, $[M+H]^{1+}$), 509.30265.

[0490] Step B: *tert*-butyl N^1-hexyl-L-α-glutaminate

HRMS: calcd for $C_{15}H_{30}N_2O_3$ + H+, 287.23292; found (ESI-FTMS, $[M+H]^{1+}$), 287.23282.

[0491] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-hexyl-L-α-glutaminate

MS (ESI) *m/z* 467.2; MS (ESI) *m/z* 933.4; HRMS: calcd for $C_{28}H_{38}N_2O_4$ + H+, 467.29043; found (ESI-FTMS, $[M+H]^{1+}$), 467.29169.

[0492] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-hexyl-L-α-glutamine

MS (ESI) *m/z* 411.1; MS (ESI) *m/z* 821.3; HRMS: calcd for $C_{24}H_{30}N_2O_4$ + H+, 411.22783; found (ESI-FTMS, $[M+H]^{1+}$), 411.22833.

Example 8WWW: N^2-(biphenyl-4-ylcarbonyl)-N^1-(5-hydroxypentyl)-L-α-glutamine

[0493] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(5-hydroxypentyl)-L-α-glutaminate

MS (ESI) *m/z* 511.2; MS (ESI) *m/z* 1021.4; HRMS: calcd for $C_{29}H_{38}N_2O_6$ + H+, 511.28026; found (ESI-FTMS, $[M+H]^{1+}$), 511.28078.

[0494] Step B: *tert*-butyl N^1-(5-hydroxypentyl)-L-α-glutaminate

HRMS: calcd for $C_{14}H_{28}N_2O_4$ + H+, 289.21218; found (ESI-FTMS, $[M+H]^{1+}$), 289.21245.

[0495] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(5-hydroxypentyl)-L-α-glutaminate

HRMS: calcd for $C_{27}H_{36}N_2O_5$ + H+, 469.26970; found (ESI-FTMS, $[M+H]^{1+}$), 469.27133.

[0496] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(5-hydroxypentyl)-L-α-glutamine

HRMS: calcd for $C_{23}H_{28}N_2O_5$ + H+, 413.20710; found (ESI-FTMS, $[M+H]^{1+}$), 413.20657.

Example 8XXX: N^2-(biphenyl-4-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine

[0497] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(6-hydroxyhexyl)-L-α-glutaminate

MS (ESI) *m/z* 525.2; MS (ESI) *m/z* 1049.4; HRMS: calcd for $C_{30}H_{40}N_2O_6$ + Na+, 547.27786; found (ESI-FTMS, $[M+Na]^{1+}$), 547.27869.

[0498] Step B: *tert*-butyl N^1-(6-hydroxyhexyl)-L-α-glutaminate

HRMS: calcd for $C_{15}H_{30}N_2O_4$ + H+, 303.22783; found (ESI-FTMS, $[M+H]^{1+}$), 303.22841.

[0499] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutaminate

HRMS: calcd for $C_{28}H_{38}N_2O_5$ + H+, 483.28535; found (ESI-FTMS, $[M+H]^{1+}$), 483.28725.

[0500] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine

HRMS: calcd for $C_{24}H_{30}N_2O_5$ + H+, 427.22275; found (ESI-FTMS, $[M+H]^{1+}$), 427.22304.

Example 8YYY: N^2-(biphenyl-4-ylcarbonyl)-N^1-propyl-L-α-glutamine

[0501] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-propyl-L-α-glutaminate

MS (ESI) *m/z* 467.1; MS (ESI) *m/z* 933.1; MS (ESI) *m/z* 955.1; HRMS: calcd for $C_{27}H_{34}N_2O_5$ + H+, 467.25405; found (ESI-FTMS, $[M+H]^{1+}$), 467.25527.

[0502] Step B: *tert*-butyl N^1-propyl-L-α-glutaminate

MS (ESI) *m/z* 245.1; MS (ESI) *m/z* 489.2; HRMS: calcd for $C_{12}H_{24}N_2O_3$ + H+, 245.18597; found (ESI-FTMS, $[M+H]^{1+}$), 245.1861.

[0503] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-propyl-L-α-glutaminate

HRMS: calcd for $C_{25}H_{32}N_2O_4$ + H+, 425.24348; found (ESI-FTMS, $[M+H]^{1+}$), 425.24455.

[0504] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-propyl-L-α-glutamine

HRMS: calcd for $C_{21}H_{24}N_2O_4$ + H+, 369.18088; found (ESI-FTMS, $[M+H]^{1+}$), 369.18091.

Example 8ZZZ: N^2-(biphenyl-4-ylcarbonyl)-N^1-[4-(dimethylamino)benzyl]-L-α-glutamine

[0505] Step A: *tert*-butyl N^1-[4-(dimethylamino)benzyl]-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 558.2; HRMS: calcd for $C_{33}H_{39}N_3O_5$ + H+, 558.29625; found (ESI-FTMS, $[M+H]^{1+}$), 558.29668.

[0506] Step B: *tert*-butyl N^1-[4-(dimethylamino)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 336.2; MS (ESI) *m/z* 671.3; HRMS: calcd for $C_{18}H_{29}N_3O_3$ + H+, 336.22817; found (ESI-FTMS, $[M+H]^{1+}$), 336.22836.

[0507] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[4-(dimethylamino)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 516.2; HRMS: calcd for $C_{31}H_{37}N_3O_4$ + H+, 516.28568; found (ESI-FTMS, $[M+H]^{1+}$), 516.28631.

[0508] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-[4-(dimethylamino)benzyl]-L-α-glutamine

MS (ESI) *m/z* 460.1; HRMS: calcd for $C_{27}H_{29}N_3O_4$ + H+, 460.22308; found (ESI-FTMS, $[M+H]^{1+}$), 460.22347.

Example 8AAAA: N^1-(4-aminobenzyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

[0509] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(4-nitrobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 560.3; MS (ESI) *m/z* 1119.5; HRMS: calcd for $C_{31}H_{33}N_3O_7$ + H+, 560.23913; found (ESI_FTMS, $[M+H]^{1+}$), 560.23944.

[0510] Step B: *tert*-butyl N^1-(4-nitrobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 338.2; HRMS: calcd for $C_{16}H_{23}N_3O_5$ + H+, 338.17105; found (ESI-FTMS, $[M+H]^{1+}$), 338.17116.

[0511] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-nitrobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 518.2; MS (ESI) *m/z* 1035.5; HRMS: calcd for $C_{29}H_{31}N_3O_6$ + H+, 518.22856; found (ESI-FTMS, $[M+H]^{1+}$), 518.22861.

[0512] Step C': Reductive alkylation of *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-nitrobenzyl)-L-α-glutaminate with 30 % formalin in water and 10 % Pd/C gave *tert*-butyl N^1-(4-aminobenzyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutaminate

MS (ESI) *m/z* 488.2; MS (ESI) *m/z* 975.4; HRMS: calcd for $C_{29}H_{33}N_3O_4$ + H+, 488.25438; found (ESI_FTMS, $[M+H]^{1+}$), 488.2542.

[0513] Step D: N^1-(4-aminobenzyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

MS (ESI) *m/z* 432.2; HRMS: calcd for $C_{25}H_{25}N_3O_4$ + H+, 432.19178; found (ESI_FTMS, $[M+H]^{1+}$), 432.1915.

Example 8BBBB: N^2-(biphenyl-4-ylcarbonyl)-N^1-[3-(dimethylamino)benzyl]-L-α-glutamine

[0514] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(3-nitrobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 560.3; MS (ESI) *m/z* 1119.4; HRMS: calcd for $C_{31}H_{33}N_3O_7$ + H+, 560.23913; found (ESI_FTMS, $[M+H]^{1+}$), 560.23892.

[0515] Step B: *tert*-butyl N^1-(3-nitrobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 338.1; MS (ESI) *m/z* 675.3; HRMS: calcd for $C_{16}H_{23}N_3O_5$ + H+, 338.17105; found (ESI-FTMS, $[M+H]^{1+}$), 338.17102.

[0516] Step C: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-nitrobenzyl)-L-α-glutaminate

MS (ESI) *m/z* 518.2; MS (ESI) *m/z* 1035.4; HRMS: calcd for $C_{29}H_{31}N_3O_6$ + H+, 518.22856; found (ESI-FTMS, $[M+H]^{1+}$), 518.22868.

[0517] Step C': Reductive alkylation of *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-nitrobenzyl)-L-α-glutaminate 30 % formalin and 10% Pd/C gave *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[3-(dimethylamino)benzyl]-L-α-glutaminate

MS (ESI) *m/z* 516.2; HRMS: calcd for $C_{31}H_{37}N_3O_4$ + H+, 516.28568; found (ESI-FTMS, $[M+H]^{1+}$), 516.28548.

[0518] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-[3-(dimethylamino)benzyl]-L-α-glutamine

MS (ESI) *m/z* 460.3; HRMS: calcd for $C_{27}H_{29}N_3O_4$ + H+, 460.22308; found (ESI-FTMS, $[M+H]^{1+}$), 460.22304.

Example 8CCCC: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-nitrobenzyl)-L-α-glutamine

[0519] MS (ESI) *m/z* 462.2; MS (ESI) *m/z* 923.2; HRMS: calcd for $C_{25}H_{23}N_3O_6$ + H+, 462.16596; found (ESI_FTMS, $[M+H]^{1+}$), 462.16599.

Example 8DDDD: N^1-(3-aminobenzyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

[0520] HRMS: calcd for $C_{25}H_{25}N_3O_4$ + H+, 432.19178; found (ESI_FTMS, $[M+H]^{1+}$), 432.1917.

Example 8EEEE: N^1-benzyl- N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

[0521] Step A: *tert*-butyl N^1-benzyl-N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 458 (M-tBut).

[0522] Step B: *tert*-butyl N^1-benzyl-L-α-glutaminate

MS (ESI) *m/z* 293.

[0523] Step C: *tert*-butyl N^1-benzyl-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutaminate

MS (ESI) *m/z* 473.

[0524] Step D: N^1-benzyl-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

MS (ESI) *m/z* 417.

Example 8FFFF: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-D-α-glutamine

[0525] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-D-α-glutaminate

Described as above according to the procedure of Example 7, except Fmoc-D-Glu-(OtBu)-OH was used as starting material for the first step. HRMS: calcd for $C_{34}H_{39}FN_2O_5$ + H+, 575.29158; found (ESI-FTMS, $[M+H]^{1+}$), 575.2927.

[0526] Step B: *tert*-butyl N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-D-α-glutaminate

HRMS: calcd for $C_{19}H_{29}FN_2O_3$ + H+, 353.22350; found (ESI-FTMS, $[M+H]^{1+}$), 353.22483.

[0527] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-D-α-glutaminate

HRMS: calcd for $C_{32}H_{37}FN_2O_4$ + H+, 533.28101; found (ESI-FTMS, $[M+H]^{1+}$), 533.28347.

[0528] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-D-α-glutamine

MS (ESI) *m/z* 477.1; MS (ESI) *m/z* 499; MS (ESI) *m/z* 953.1; HRMS: calcd for $C_{28}H_{29}FN_2O_4$ + H+, 477.21841; found (ESI-FTMS, $[M+H]^{1+}$), 477.21815.

Example 8GGGG: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-α-glutamine

[0529] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-α-glutaminate

Described as above according to the procedure of Example 7, except Fmoc-DL-Glu-(OtBu)-OH (racemic mixture) was used as starting material for the first step. HRMS: calcd for $C_{34}H_{39}FN_2O_5$ + H+, 575.29158; found (ESI-FTMS, $[M+H]^{1+}$), 575.29217.

[0530] Step B: *tert*-butyl N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-α-glutaminate

HRMS: calcd for $C_{19}H_{29}FN_2O_3$ + H+, 353.22350; found (ESI-FTMS, $[M+H]^{1+}$), 353.22429.

[0531] Step C: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-α-glutaminate

HRMS: calcd for $C_{32}H_{37}FN_2O_4$ + H+, 533.28101; found (ESI-FTMS, $[M+H]^{1+}$), 533.28268.

[0532] Step D: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-α-glutamine

MS (ESI) *m/z* 477.1; MS (ESI) *m/z* 953.1; HRMS: calcd for $C_{28}H_{29}FN_2O_4$ + H+, 477.21841; found (ESI-FTMS, $[M+H]^{1+}$), 477.21805.

Example 8HHHH: 4-Benzylcarbamoyl-4-[4-(pyrimidin-2-ylamino)-benzoylamino-butyric acid tert-butyric acid

[0533] Step C: 4-Benzylcarbamoyl-4-[4-(pyrimidin-2-ylamino)-benzoylamino-butyric acid tert-butyl ester

MS (ESI) *m/z* 488.

[0534] Step D: 4-Benzylcarbamoyl-4-[4-(pyrimidin-2-ylamino)-benzoylamino-butyric acid tert-butyric acid

MS (ESI) *m/z* 432.

Example 8IIII: N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine

[0535] Step A: *tert*-butyl N^2-[(9H-fluoren-9-ylmethoxy)carbonyl]- N^1-(3-phenylpropyl)-L-α-glutaminate

1,9(Fmoc)L-glutamic acid -*tert*-butylester monohydrate (1.33g, 3.00mmol) was dissolved in DMF (8mL) under nitrogen. BOP (1.33g, 3.00mmol) was added as a solid, followed by 3-phenyl-1-propylamine (427mL, 3mmol). Finally DIEA (627mL, 3.6mmol) was added dropwise. The reaction was monitored by TLC, and stirred for 24 hrs. The

reaction mixture was then added to stirring H_2O (400mL). After stirring for 1 hour, clumps of white solid were formed. The clumps were broken up with a spatula and stirred for an additional 30 minutes. The solid was filtered and washed with H_2O. The solid was then dissolved in CH_2Cl_2 and dried with Na_2SO4. The solution was filtered and concentrated, leaving a white solid. The solid was dissolved in minimal acetone and hexanes were added. The solvents were then removed and the white solid was dried under vacuum. Yield 1.58g of *tert*-butyl N^2-[(9H-fluoren-9-ylmethoxy)carbonyl]- N^1-(3-phenylpropyl)-L-α-glutaminate at 97% yield.

MS (ESI) *m/z* 543.3; HRMS: calcd for $C_{33}H_{38}N_2O_5$ + H+, 543.2853; found (ESI-FTMS, $[M+H]^{1+}$), 543.2847.

[0536] Step B: *tert*-butyl N^1-(3-phenylpropyl)-L-α-glutaminate

Tert-butyl N^2-[(9H-fluoren-9-ylmethoxy)carbonyl]-N^1-(3-phenylpropyl)-L-α-glutaminate (1.5g, 2.76mmol) was partially dissolved in CH_3CN (15mL). DEA (2.9mL, 27.6mmol) was added, which was fully dissolved within 10 minutes. The reaction was monitored by TLC and was complete at 2 hrs. The solvent was removed and the remaining material dried under vacuum. The material was purified on a short silica column using 5%Acetone/CH_2Cl_2 to elute the Fmoc by-product and then 50%Acetone/CH_2Cl_2 to elute the product. The clear oil present at the end was dried shortly under vacuum, and then taken to the next step immediately. It was never fully solvent free so the yield of *tert*-butyl N^1-(3-phenylpropyl)-L-α-glutaminate was 1.65g, and was assumed to be quantitative. MS (ESI) *m/z* 321.2; MS (ESI) *m/z* 641.4; HRMS: calcd for $C_{18}H_{28}N_2O_3$ + H+, 321.2173; found (ESI-FTMS, $[M+H]^{1+}$), 321.2167.

[0537] Step C: *tert*-butyl N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutaminate

T*ert*-butyl N^1-(3-phenylpropyl)-L-α-glutaminate (350mg, 1.09mmol) was dissolved in DMF (5mL), in a 20mL vial under nitrogen. 2-Fluorenecarboxylic acid (229mg, 1.09mmol) and BOP (530mg, 1.20mmol) were added as solids and dissolved. Finally DIEA (228mL, 1.31mmol) was added, and the reaction stirred overnight. Monitored by TLC, the reaction was complete after stirring overnight. The reaction mixture was added to H_2O (100mL), precipitating a pale yellow solid. The solid was filtered and dried in a dessicator overnight. Once dry, the solid was taken up in a small amount of acetone, and hexanes were added to precipitate a pale yellow solid. The solid was filtered, washed

with hexanes and dried in a dessicator. Yield 293mg of *tert*-butyl N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutaminate at 52% yield. MS (ESI) *m/z* 513.3; MS (ESI) *m/z* 1025.6; MS (ESI) *m/z* 535.3; HRMS: calcd for $C_{32}H_{36}N_2O_4$ + H+, 513.27478; found (ESI-FTMS, $[M+H]^{1+}$), 513.2766.

[0538] Step D: N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine *Tert*-butyl N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutaminate (273mg, 0.533mmol) was dissolved in CH_2Cl_2 (1.5mL). TFA (1.23mL, 16.0mmol) was diluted in CH_2Cl_2 (2mL) and was then slowly added to the first solution. The reaction was monitored by TLC and complete at 2 hrs. The solvent was removed with a nitrogen blower and the remaining yellow oil dried under vacuum. The yellow oil was then dissolved in minimal acetone and hexanes was added precipitating a white solid. The solid was filtered, washed with hexanes and then dried under vacuum. The reaction yielded 194mg of N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine at an 80% yield. MS (ESI) *m/z* 457.3; MS (ESI) *m/z* 913.5.

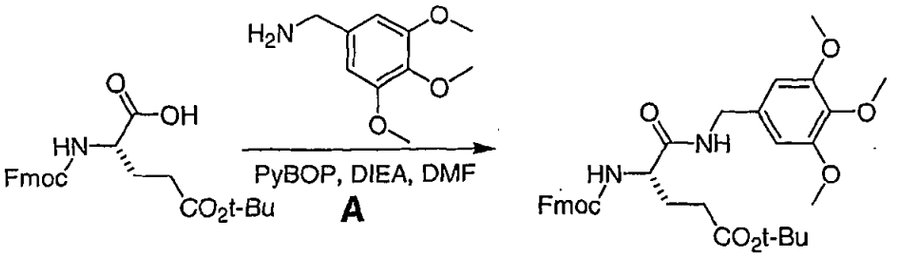
Example 8JJJJ: N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine

[0539] Step C: *tert*-butyl N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutaminate

MS (ESI) *m/z* 513.3; MS (ESI) *m/z* 1025.6; HRMS: calcd for $C_{32}H_{36}N_2O_4$ + H+, 513.27478; found (ESI-FTMS, $[M+H]^{1+}$), 513.27653.

[0540] Step D: N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine MS (ESI) *m/z* 457.3; MS (ESI) *m/z* 913.5; MS (ESI) *m/z* 479.3.

Example 8KKKK: N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine



[0541] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 605.2; MS (ESI) *m/z* 1209.4; HRMS: calcd for $C_{34}H_{40}N_2O_8$ + H+, 605.28574; found (ESI_FT, $[M+H]^{1+}$), 605.28453.

[0542] Step B: *tert*-butyl N^1-(3,4,5-trimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 383.1; MS (ESI) *m/z* 765.3; HRMS: calcd for $C_{19}H_{30}N_2O_6$ + H+, 383.21766; found (ESI_FT, $[M+H]^{1+}$), 383.21755.

[0543] Step C: *tert*-butyl N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 575.4; MS (ESI) *m/z* 1149.7; HRMS: calcd for $C_{33}H_{38}N_2O_7$ + H+, 575.27518; found (ESI-FTMS, $[M+H]^{1+}$), 575.27604.

[0544] Step D: N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine

MS (ESI) *m/z* 519.3; MS (ESI) *m/z* 1037.6; HRMS: calcd for $C_{29}H_{30}N_2O_7$ + H+, 519.21258; found (ESI-FTMS, $[M+H]^{1+}$), 519.2133.

Example 8LLLL: N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0545] Step C: *tert*-butyl N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 575.4; MS (ESI) *m/z* 1149.7; HRMS: calcd for $C_{33}H_{38}N_2O_7$ + H+, 575.27518; found (ESI-FTMS, $[M+H]^{1+}$), 575.2761.

[0546] Step D: N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine

MS (ESI) *m/z* 519.3; MS (ESI) *m/z* 1037.6; MS (ESI) *m/z* 541.3; HRMS: calcd for $C_{29}H_{30}N_2O_7$ + H+, 519.21258; found (ESI-FTMS, $[M+H]^{1+}$), 519.21329.

Example 8MMMM: N^2-[(9-oxo-9*H*-fluoren-2-yl)carbonyl]-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0547] Step C: *tert*-butyl N^2-[(9-oxo-9*H*-fluoren-2-yl)carbonyl]-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 589.4; MS (ESI) *m/z* 1177.7; MS (ESI) *m/z* 606.4; HRMS: calcd for $C_{33}H_{36}N_2O_8$ + H+, 589.25444; found (ESI-FTMS, $[M+H]^{1+}$), 589.25507.

[0548] Step D: N^2-[(9-oxo-9*H*-fluoren-2-yl)carbonyl]-N^1-(3,4,5-

trimethoxybenzyl)-L-α-glutamine

MS (ESI) *m/z* 531.3; MS (ESI) *m/z* 1063.5; HRMS: calcd for $C_{29}H_{28}N_2O_8$ + H+, 533.19184; found (ESI-FTMS, $[M+H]^{1+}$), 533.19236.

Example 8NNNN: N^2-(4-phenoxybenzoyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine

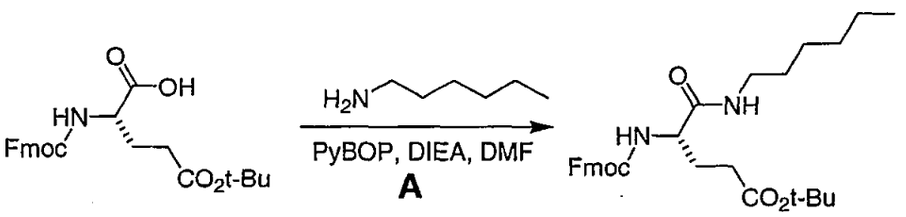
[0549] Step C: *tert*-butyl N^2-(4-phenoxybenzoyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 579.3; MS (ESI) *m/z* 1157.7; HRMS: calcd for $C_{32}H_{38}N_2O_8$ + H+, 579.27009; found (ESI-FTMS, $[M+H]^{1+}$), 579.2719.

[0550] Step D: N^2-(4-phenoxybenzoyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine

MS (ESI) *m/z* 523.3; MS (ESI) *m/z* 1045.5.

Example 8OOOO: N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-hexyl-L-α-glutamine



[0551] Step A: *tert*-butyl N^2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-N^1-hexyl-L-α-glutaminate

MS (ESI) *m/z* 509.3; MS (ESI) *m/z* 1017.5; HRMS: calcd for $C_{30}H_{40}N_2O_5$ + H+, 509.30100; found (ESI-FTMS, $[M+H]^{1+}$), 509.30265.

[0552] Step B: *tert*-butyl N^1-hexyl-L-α-glutaminate

HRMS: calcd for $C_{15}H_{30}N_2O_3$ + H+, 287.23292; found (ESI-FTMS, $[M+H]^{1+}$), 287.23282.

[0553] Step C: *tert*-butyl N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-hexyl-L-α-glutaminate

MS (ESI) *m/z* 479.1; MS (ESI) *m/z* 979.2; MS (ESI) *m/z* 501.1; HRMS: calcd for $C_{29}H_{38}N_2O_4$ + H+, 479.29043; found (ESI-FTMS, $[M+H]^{1+}$), 479.29145.

[0554] Step D: N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-hexyl-L-α-glutamine

MS (ESI) *m/z* 423.3; MS (ESI) *m/z* 845.6; MS (ESI) *m/z* 445.3.

Example 8PPPP: N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-hexyl-L-α-glutamine

[0555] Step C: *tert*-butyl N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-hexyl-L-α-glutaminate MS (ESI) *m/z* 479.1; MS (ESI) *m/z* 957.3; MS (ESI) *m/z* 979.2; HRMS: calcd for $C_{29}H_{38}N_2O_4$ + H+, 479.29043; found (ESI-FTMS, $[M+H]^{1+}$), 479.29145.

[0556] Step D: N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-hexyl-L-α-glutamine MS (ESI) *m/z* 423.3; MS (ESI) *m/z* 845.5; MS (ESI) *m/z* 445.3.

Example 8QQQQ: N^1-hexyl-N^2-(4-phenoxybenzoyl)-L-α-glutamine

[0557] Step C: *tert*-butyl N^1-hexyl-N^2-(4-phenoxybenzoyl)-L-α-glutaminate MS (ESI) *m/z* 483.1; MS (ESI) *m/z* 965.3; MS (ESI) *m/z* 987.3; HRMS: calcd for $C_{28}H_{38}N_2O_5$ + H+, 483.28535; found (ESI-FTMS, $[M+H]^{1+}$), 483.28715.

[0558] Step D: N^1-hexyl-N^2-(4-phenoxybenzoyl)-L-α-glutamine MS (ESI) *m/z* 427.3; MS (ESI) *m/z* 853.5; MS (ESI) *m/z* 449.3.

Example 8RRRR: N^1-hexyl-N^2-[(9-oxo-9*H*-fluoren-2-yl)carbonyl]-L-α-glutamine

[0559] Step C: *tert*-butyl N^1-hexyl-N^2-[(9-oxo-9*H*-fluoren-2-yl)carbonyl]-L-α-glutaminate MS (ESI) *m/z* 493.1; MS (ESI) *m/z* 985.3; HRMS: calcd for $C_{29}H_{36}N_2O_5$ + H+, 493.26970; found (ESI-FTMS, $[M+H]^{1+}$), 493.27119.

[0560] Step D: N^1-hexyl-N^2-[(9-oxo-9*H*-fluoren-2-yl)carbonyl]-L-α-glutamine MS (ESI) *m/z* 437.3; MS (ESI) *m/z* 873.5; MS (ESI) *m/z* 1309.8.

Example 8SSSS: N^2-(4-benzoylbenzoyl)-N^1-benzyl-L-α-glutamine

[0561] Step C: *tert*-butyl N^2-(4-benzoylbenzoyl)-N^1-benzyl-L-α-glutaminate MS (ESI) *m/z* 501.2; MS (ESI) *m/z* 523.2; HRMS: calcd for $C_{30}H_{32}N_2O_5$ + H+, 501.23840; found (ESI+, $[M+H]^{1+}$), 501.23859.

[0562] Step D: N^2-(4-benzoylbenzoyl)-N^1-benzyl-L-α-glutamine MS (ESI) *m/z* 445.2; HRMS: calcd for $C_{26}H_{24}N_2O_5$ + H+, 445.17580; found (ESI+, $[M+H]^{1+}$), 445.17619.

Example 8TTTT: N^1-(6-hydroxyhexyl)-N^2-(4-phenoxybenzoyl)-L-α-glutamine

[0563] MS (ESI) m/z 443.2; MS (ESI) m/z 885.5; HRMS: calcd for $C_{24}H_{30}N_2O_6$ + H+, 443.21766; found (ESI-FTMS, $[M+H]^{1+}$), 443.21905.

Example 8UUUU: N^2-(9H-fluoren-9-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine

[0564] MS (ESI) m/z 437.3; MS (ESI) m/z 551.3; HRMS: calcd for $C_{25}H_{30}N_2O_5$ + H+, 439.22275; found (ESI-FTMS, $[M+H]^{1+}$), 439.22374.

Example 8VVVV: N^2-(9H-fluoren-9-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0565] MS (ESI) m/z 519.1; MS (ESI) m/z 1037.2; MS (ESI) m/z 536.1; HRMS: calcd for $C_{29}H_{30}N_2O_7$ + H+, 519.21258; found (ESI-FTMS, $[M+H]^{1+}$), 519.213.

Example 8WWWW: N^2-(3-phenoxybenzoyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0566] MS (ESI) m/z 523.1; MS (ESI) m/z 1045.2; MS (ESI) m/z 545.1; HRMS: calcd for $C_{28}H_{30}N_2O_8$ + H+, 523.20749; found (ESI-FTMS, $[M+H]^{1+}$), 523.20712.

Example 8XXXX: N^2-(9H-fluoren-4-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0567] MS (ESI) m/z 519.1; MS (ESI) m/z 1037.2; HRMS: calcd for $C_{29}H_{30}N_2O_7$ + H+, 519.21258; found (ESI-FTMS, $[M+H]^{1+}$), 519.21308.

Example 8YYYY: N^1-1-adamantyl-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine

[0568] MS (ESI) m/z 485.3; MS (ESI) m/z 971.6; MS (ESI) m/z 521.3; HRMS: calcd for $C_{29}H_{30}N_2O_5$ + H+, 487.22275; found (ESI-FTMS, $[M+H]^{1+}$), 487.22272.

Example 8ZZZZ: N^1-1-adamantyl-N^2-(4-phenoxybenzoyl)-L-α-glutamine

[0569] MS (ESI) m/z 477.1; MS (ESI) m/z 953.3; MS (ESI) m/z 499.1; HRMS: calcd for $C_{28}H_{32}N_2O_5$ + H+, 477.23840; found (ESI-FTMS, $[M+H]^{1+}$), 477.23857.

Example 8AAAAA: N^1-1-adamantyl-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine

[0570] MS (ESI) m/z 473.3; MS (ESI) m/z 945.5; HRMS: calcd for $C_{29}H_{32}N_2O_4$ + H+, 473.24348; found (ESI-FTMS, $[M+H]^{1+}$), 473.24374.

Example 8BBBBB: N^1-1-adamantyl-N^2-(9H-fluoren-9-ylcarbonyl)-L-α-glutamine

[0571] MS (ESI) m/z 471.3; MS (ESI) m/z 585.3; MS (ESI) m/z 943.6; HRMS: calcd for $C_{29}H_{32}N_2O_4$ + H+, 473.24348; found (ESI-FTMS, $[M+H]^{1+}$), 473.2437.

Example 8CCCCC: N^2-(9H-fluoren-2-ylcarbonyl)-N^1-(3-methylbenzyl)-L-α-glutamine

[0572] HRMS: calcd for $C_{27}H_{26}N_2O_4$ + H+, 443.19653; found (ESI-FTMS, $[M+H]^{1+}$), 443.1974.

Example 8DDDDD: N^1-(3-methylbenzyl)-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine

[0573] HRMS: calcd for $C_{27}H_{24}N_2O_5$ + H+, 457.17580; found (ESI-FTMS, $[M+H]^{1+}$), 457.17616.

Example 8EEEEE: N^2-(9H-fluoren-9-ylcarbonyl)-N^1-(3-methylbenzyl)-L-α-glutamine

[0574] HRMS: calcd for $C_{27}H_{26}N_2O_4$ + H+, 443.19653; found (ESI-FTMS, $[M+H]^{1+}$), 443.19709.

Example 8FFFFF: N^2-(9H-fluoren-2-ylcarbonyl)-N^1-propyl-L-α-glutamine

[0575] HRMS: calcd for $C_{22}H_{24}N_2O_4$ + H+, 381.18088; found (ESI-FTMS, $[M+H]^{1+}$), 381.18117.

Example 8GGGGG: 4-[(9H-fluoren-9-carbonyl)-amino]-4-propylcarbamoyl-butyric acid

[0576] MS (ESI) m/z 395.1; MS (ESI) m/z 789.2; MS (ESI) m/z 811.2; HRMS: calcd for $C_{22}H_{24}N_2O_4$ + H+, 381.18088; found (ESI-FTMS, $[M+H]^{1+}$), 395.16097.

Example 8HHHHH: 4-[(9-Oxo-9H-fluorene-2-carbonyl)-amino]-4-propylcarbamoyl-butyric acid

[0577] MS (ESI) m/z 381.1; MS (ESI) m/z 403.1; MS (ESI) m/z 761.2; HRMS: calcd for $C_{22}H_{22}N_2O_5$ + H+, 395.16015; found (ESI-FTMS, $[M+H]^{1+}$), 381.18165.

Example 8IIIII: N^1-benzyl-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine

[0578] MS (ESI) m/z 441.2; MS (ESI) m/z 883.3; HRMS: calcd for $C_{26}H_{22}N_2O_5$ + H+, 443.16015; found (ESI-FTMS, $[M+H]^{1+}$), 443.16063.

Example 8JJJJJ: N^1-benzyl-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine

[0579] MS (ESI) m/z 427.2; MS (ESI) m/z 855.3; HRMS: calcd for $C_{26}H_{24}N_2O_4$ + H+, 429.18088; found (ESI-FTMS, $[M+H]^{1+}$), 429.18148.

Example 8KKKKK: N^1-benzyl-N^2-(9H-fluoren-9-ylcarbonyl)-L-α-glutamine

[0580] MS (ESI) m/z 429; MS (ESI) m/z 857; MS (ESI) m/z 451; HRMS: calcd for $C_{26}H_{24}N_2O_4$ + H+, 429.18088; found (ESI-FTMS, $[M+H]^{1+}$), 429.1815.

Example 8LLLLL: N^1-benzyl-N^2-(3-phenoxybenzoyl)-L-α-glutamine

[0581] MS (ESI) m/z 433; MS (ESI) m/z 455; MS (ESI) m/z 865; HRMS: calcd for $C_{25}H_{24}N_2O_5$ + H+, 433.17580; found (ESI-FTMS, $[M+H]^{1+}$), 433.17696.

Example 8MMMMM: N^1-(1-methyl-1-phenylethyl)-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine

[0582] MS (ESI) m/z 471.2; MS (ESI) m/z 941.5; MS (ESI) m/z 493.2; HRMS: calcd for $C_{28}H_{26}N_2O_5$ + H+, 471.19145; found (ESI-FTMS, $[M+H]^{1+}$), 471.19271.

Example 8NNNNN: N^2-(9H-fluoren-9-ylcarbonyl)-N^1-(1-methyl-1-phenylethyl)-L-α-glutamine

[0583] MS (ESI) m/z 455.1; MS (ESI) m/z 911.3; HRMS: calcd for $C_{28}H_{28}N_2O_4$ + H+, 457.21218; found (ESI-FTMS, $[M+H]^{1+}$), 457.214.

Example 8OOOOO: N^1-(1-methyl-1-phenylethyl)-N^2-(3-phenoxybenzoyl)-L-α-glutamine

[0584] MS (ESI) m/z 461.2; MS (ESI) m/z 921.5; MS (ESI) m/z 483.2; HRMS: calcd for $C_{27}H_{28}N_2O_5$ + H+, 461.20710; found (ESI-FTMS, $[M+H]^{1+}$), 461.20882.

Example 8PPPPP: N^2-(biphenyl-4-ylcarbonyl)-N^1-[(1S)-1-phenylethyl]-L-α-glutamine

[0585] MS (ESI) m/z 431.2; MS (ESI) m/z 861.4; MS (ESI) m/z 453.2; HRMS: calcd for $C_{26}H_{26}N_2O_4$ + H+, 431.19653; found (ESI-FTMS, $[M+H]^{1+}$), 431.19802.

Example 8QQQQQ: N^2-(9H-fluoren-2-ylcarbonyl)-N^1-[(1S)-1-phenylethyl]-L-α-glutamine

[0586] MS (ESI) m/z 443.2; MS (ESI) m/z 885.4; MS (ESI) m/z 465.2; HRMS: calcd for $C_{27}H_{26}N_2O_4$ + H+, 443.19653; found (ESI-FTMS, $[M+H]^{1+}$), 443.19772.

Example 8RRRRR: N^2-(biphenyl-4-ylcarbonyl)-N1-[(1S)-1-(4-fluorophenyl)ethyl]-L-α-glutamine

[0587] MS (ESI) m/z 449.2; MS (ESI) m/z 897.4; HRMS: calcd for $C_{26}H_{25}FN_2O_4$ + H+, 449.18711; found (ESI-FTMS, $[M+H]^{1+}$), 449.18839.

Example 8SSSSS: tert-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(1-phenylethyl)-L-α-glutaminate

[0588] MS(ESI) m/z 505.3.

Example 8TTTTT: N^2-(biphenyl-4-ylcarbonyl)-N^1-[(1R)-1-(4-fluorophenyl)ethyl]-L-α-glutamine

[0589] MS (ESI) m/z 449.2; MS (ESI) m/z 897.5; MS (ESI) m/z 471.2; HRMS: calcd for $C_{26}H_{25}FN_2O_4$ + H+, 449.18711; found (ESI-FTMS, $[M+H]^{1+}$), 449.18679.

Example 8UUUUU: N^2-(biphenyl-4-ylcarbonyl)-N^1-[(1R)-1-phenylethyl]-L-α-glutamine

[0590] MS (ESI) m/z 431.2; MS (ESI) m/z 861.5; MS (ESI) m/z 453.2; HRMS: calcd for $C_{26}H_{26}N_2O_4$ + H+, 431.19653; found (ESI-FTMS, $[M+H]^{1+}$), 431.19828.

Example 8VVVVV: N^2-(9H-fluoren-2-ylcarbonyl)-N^1-[(1R)-1-phenylethyl]-L-α-glutamine

[0591] MS (ESI) m/z 443.2; MS (ESI) m/z 885.5; MS (ESI) m/z 465.2; HRMS: calcd for $C_{27}H_{26}N_2O_4$ + H+, 443.19653; found (ESI-FTMS, $[M+H]^{1+}$), 443.19676.

Example 8WWWWW: N^2-(9H-fluoren-1-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine

[0592] MS (ESI) m/z 437.3; MS (ESI) m/z 875.5; HRMS: calcd for $C_{25}H_{30}N_2O_5$ + H+, 439.22275; found (ESI-FTMS, $[M+H]^{1+}$), 439.22313.

Example 8XXXXX: N^1-(6-hydroxyhexyl)-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine

[0593] MS (ESI) m/z 453.2; HRMS: calcd for $C_{25}H_{28}N_2O_6$ + H+, 453.20201; found (ESI-FTMS, $[M+H]^{1+}$), 453.2027.

Example 8YYYYY: N^2-(biphenyl-4-ylcarbonyl)-N^1-9H-fluoren-9-yl-L-α-glutamine

[0594] MS (ESI) m/z 489.1; MS (ESI) m/z 979.2; HRMS: calcd for $C_{31}H_{26}N_2O_4$ + H+, 491.19653; found (ESI-FTMS, $[M+H]^{1+}$), 491.19778.

Example 8ZZZZZ: N^2-(9H-fluoren-2-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0595] MS (ESI) m/z 489.2; MS (ESI) m/z 977.4; HRMS: calcd for $C_{29}H_{29}FN_2O_4$ + H+, 489.21841; found (ESI-FTMS, $[M+H]^{1+}$), 489.21827.

Example 8AAAAAA: N-(1-adamantylmethyl)-N^2-(biphenyl-4-ylcarbonyl)-L-α-glutamine

[0596] MS (ESI) m/z 475.2; MS (ESI) m/z 949.5; HRMS: calcd for $C_{29}H_{34}N_2O_4$ + H+, 475.25913; found (ESI-FTMS, $[M+H]^{1+}$), 475.25916.

Example 8BBBBBB: N-[(1S)-1-benzyl-2-hydroxyethyl]-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine

[0597] MS (ESI) m/z 473.2; MS (ESI) m/z 945.4; HRMS: calcd for $C_{28}H_{28}N_2O_5$ + H+, 473.20710; found (ESI-FTMS, $[M+H]^{1+}$), 473.2073.

Example 8CCCCCC: N^2-(biphenyl-4-ylcarbonyl)-N-methyl-N-(2-phenylethyl)-L-α-glutamine

[0598] MS (ESI) m/z 445.4; MS (ESI) m/z 889.7; HRMS: calcd for $C_{27}H_{28}N_2O_4$ + H+, 445.21218; found (ESI-FTMS, $[M+H]^{1+}$), 445.21312.

Example 8DDDDDD: N^2-(9H-fluoren-2-ylcarbonyl)-N-methyl-N-(2-phenylethyl)-L-α-glutamine

MS (ESI) m/z 457.4; MS (ESI) m/z 913.7; HRMS: calcd for $C_{28}H_{28}N_2O_4$ + H+, 457.21218; found (ESI-FTMS, $[M+H]^{1+}$), 457.21146.

Example 8EEEEEE: N^2-(biphenyl-4-ylcarbonyl)-N-butyl-N-methyl-L-α-glutamine

[0599] MS (ESI) m/z 397.2; MS (ESI) m/z 793.4; MS (ESI) m/z 419.2; HRMS: calcd for $C_{23}H_{28}N_2O_4$ + H+, 397.21218; found (ESI-FTMS, $[M+H]^{1+}$), 397.21249.

Example 8FFFFFF: N-butyl-N^2-(9H-fluoren-2-ylcarbonyl)-N-methyl-L-α-glutamine

[0600] MS (ESI) m/z 409.3; MS (ESI) m/z 817.5; HRMS: calcd for $C_{24}H_{28}N_2O_4$ + H+, 409.21218; found (ESI-FTMS, $[M+H]^{1+}$), 409.21227.

Example 8GGGGGG: N^2-(biphenyl-4-ylcarbonyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methyl-L-α-glutamine

[0601] MS (ESI) m/z 505.3; MS (ESI) m/z 527.3; MS (ESI) m/z 1009.6; HRMS: calcd for $C_{29}H_{32}N_2O_6$ + H+, 505.23331; found (ESI-FTMS, $[M+H]^{1+}$), 505.23512.

Example 8HHHHHH: N^2-[4-(1,3-benzodioxol-5-yl)benzoyl]-N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0602] MS (ESI) m/z 521.1; MS (ESI) m/z 1041.3; HRMS: calcd for $C_{29}H_{29}FN_2O_6$ + H+, 521.20824; found (ESI-FTMS, $[M+H]^{1+}$), 521.20872.

Example 8IIIIII: N-[2-(3,4-dimethoxyphenyl)ethyl]-N^2-(9H-fluoren-2-ylcarbonyl)-N-methyl-L-α-glutamine

[0603] MS (ESI) m/z 517.2; MS (ESI) m/z 1033.3; HRMS: calcd for $C_{30}H_{32}N_2O_6$ + H+, 517.23331; found (ESI-FTMS, $[M+H]^{1+}$), 517.23342.

Example 8JJJJJJJ: N^2-(9H-fluoren-2-ylcarbonyl)-N-[(2R)-2-phenylpropyl]-L-α-glutamine

[0604] MS (ESI) m/z 457.2; MS (ESI) m/z 913.3; MS (ESI) m/z 479.1; HRMS: calcd for $C_{28}H_{28}N_2O_4$ + H+, 457.21218; found (ESI-FTMS, $[M+H]^{1+}$), 457.21246.

Example 8KKKKKK: N^2-(biphenyl-4-ylcarbonyl)-N-[(2R)-2-phenylpropyl]-L-α-glutamine

[0605] MS (ESI) m/z 445.2; MS (ESI) m/z 889.3; HRMS: calcd for $C_{27}H_{28}N_2O_4$ + H+, 445.21218; found (ESI-FTMS, $[M+H]^{1+}$), 445.21285.

Example 8LLLLLL: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-glutamamide

[0606] MS (ESI) m/z 476.2; MS (ESI) m/z 951.5; HRMS: calcd for $C_{28}H_{30}FN_3O_3$ + H+, 476.23440; found (ESI-FTMS, $[M+H]^{1+}$), 476.23543.

Example 8MMMMMM: N-[(1S)-1-benzyl-2-hydroxyethyl]-N^2-(biphenyl-4-ylcarbonyl)-L-α-glutamine

[0607] MS (ESI) m/z 461.2; MS (ESI) m/z 921.4; MS (ESI) m/z 943.4; HRMS: calcd for $C_{27}H_{28}N_2O_5$ + H+, 461.20710; found (ESI-FTMS, $[M+H]^{1+}$), 461.20748.

Example 8NNNNNN: N^1-benzyl-N^2-(4-bromobenzoyl)-L-α-glutamine

[0608] MS (ESI) m/z 419.1; MS (ESI) m/z 837.2; HRMS: calcd for $C_{19}H_{19}BrN_2O_4$ + H+, 419.06009; found (ESI_FT, $[M+H]^{1+}$), 419.05998.

Example 8OOOOOO: N^1-[2-(acetylamino)ethyl]-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

[0609] MS (ESI) m/z 410.2; MS (ESI) m/z 821.5; HRMS: calcd for $C_{22}H_{25}N_3O5$ + H+, 412.18670; found (ESI_FT, $[M+H]^{1+}$), 412.18628.

Example 8PPPPPP: N^2-(1,1'-biphenyl-4-ylacetyl)-N^1-(3-methoxybenzyl)-L-α-glutamine

[0610] The title compound was prepared according to procedures similar to those described in Example 7, except biphenylacetic acid was used. MS (ESI) m/z 461.2; MS (ESI) m/z 921.4; HRMS: calcd for $C_{27}H_{28}N_2O_5$ + H+, 461.20710; found (ESI_FTMS, $[M+H]^{1+}$), 461.20514.

Example 8QQQQQQ: N^1-(2-benzylphenyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine

[0611] MS (ESI-) m/z 491.3; HRMS: calcd for $C_{31}H_{28}N_2O_4$ + H+, 493.21218; found (ESI-FTMS, $[M+H]^{1+}$), 493.21319.

Example 8RRRRRR: N^2-2-naphthoyl-N^1-(3-phenylpropyl)-L-α-glutamine

[0612] MS (ESI) m/z 419.1; MS (ESI) m/z 837.1; MS (ESI) m/z 441.1; HRMS: calcd for $C_{25}H_{26}N_2O_4$ + H+, 419.19653; found (ESI-FTMS, $[M+H]^{1+}$), 419.19678.

Example 8SSSSSS: N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-N^1-(3-phenylpropyl)-L-α-glutamine

[0613] MS (ESI) m/z 471.3; MS (ESI) m/z 941.5; HRMS: calcd for $C_{28}H_{26}N_2O_5$ + H+, 471.19145; found (ESI-FTMS, $[M+H]^{1+}$), 471.19142.

Example 8TTTTTT: N^2-(4-phenoxybenzoyl)-N^1-(3-phenylpropyl)-L-α-glutamine

[0614] HRMS: calcd for $C_{27}H_{28}N_2O_5$ + H+, 461.20710; found (ESI-FTMS, $[M+H]^{1+}$), 461.20673.

Example 8UUUUUU: N^1-benzyl-N^2-[4-(pyrimidin-2-ylamino)benzoyl]-L-α-glutamine

[0615] MS m/z 02-101699GMS.

Example 8VVVVVV: N^2-(9H-fluoren-2-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine

[0616] MS (ESI) m/z 439.2; HRMS: calcd for $C_{25}H_{30}N_2O_5$ + H+, 439.22275; found (ESI-FTMS, $[M+H]^{1+}$), 439.22379.

Example 8WWWWWW: N^2-[4-(5-bromo-2-thienyl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0617] MS (ESI) *m/z* 561.3; MS (ESI) *m/z* 1121.5; HRMS: calcd for $C_{26}H_{26}BrFN_2O_4S$ + H+, 561.08534; found (ESI-FTMS, $[M+H]^{1+}$), 561.08472.

Example 8XXXXXX: *N*-[2-(5-chloro-2-thienyl)-1,1-dimethylethyl]-N^2-[(3'-fluorobiphenyl-4-yl)carbonyl]-L-α-glutamine

[0618] MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1033.5; MS (ESI) *m/z* 539.3; HRMS: calcd for $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; found (ESI-FTMS, $[M+H]^{1+}$), 517.13517.

[0619] MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1033.6; MS (ESI) *m/z* 539.3; HRMS: calcd for $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; found (ESI-FTMS, $[M+H]^{1+}$), 517.13686.

Example 8YYYYYY: N^2-[(3',4'-difluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0620] MS (ESI) *m/z* 513.4; MS (ESI) *m/z* 1025.7; MS (ESI) *m/z* 535.3; HRMS: calcd for $C_{28}H_{27}F_3N_2O_4$ + H+, 513.19957; found (ESI-FTMS, $[M+H]^{1+}$), 513.19837.

[0621] MS (ESI) *m/z* 513.4; MS (ESI) *m/z* 1025.8; MS (ESI) *m/z* 535.4; HRMS: calcd for $C_{28}H_{27}F_3N_2O_4$ + H+, 513.19957; found (ESI-FTMS, $[M+H]^{1+}$), 513.20152.

Example 8ZZZZZZ: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(3',4'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine

[0622] MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.5; HRMS: calcd for $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; found (ESI-FTMS, $[M+H]^{1+}$), 529.16931.

Example 8AAAAAAA: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(2',4'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine

[0623] MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.5; HRMS: calcd for $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; found (ESI-FTMS, $[M+H]^{1+}$), 529.16951.

Example 8BBBBBBB: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(2',5'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine

[0624] MS (ESI) *m/z* 529.3; MS (ESI) *m/z* 1057.5; MS (ESI) *m/z* 551.2; HRMS: calcd for $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; found (ESI-FTMS, $[M+H]^{1+}$), 529.16954.

Example 8CCCCCCC: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(2',6'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine

[0625] MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.4; HRMS: calcd for $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; found (ESI-FTMS, $[M+H]^{1+}$), 529.16943.

Example 8DDDDDDD: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(3',5'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine

[0626] MS (ESI) *m/z* 529.3; MS (ESI) *m/z* 1057.5; MS (ESI) *m/z* 551.3; HRMS: calcd for $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; found (ESI-FTMS, $[M+H]^{1+}$), 529.17191.

Example 8EEEEEEE: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(2',3'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine

[0627] HRMS: calcd for $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; found (ESI-FTMS, $[M+H]^{1+}$), 529.17167.

Example 8FFFFFFF: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-(4-pyrimidin-5-ylbenzoyl)-L-α-glutamine

[0628] MS (ESI) *m/z* 461.2; MS (ESI) *m/z* 921.4; HRMS: calcd for $C_{26}H_{28}N_4O_4$ + H+, 461.21833; found (ESI-FTMS, $[M+H]^{1+}$), 461.21863.

Example 8GGGGGGG: N^2-[(3',4'-difluorobiphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0629] MS (ESI) *m/z* 495.2; MS (ESI) *m/z* 989.4; HRMS: calcd for $C_{28}H_{28}F_2N_2O_4$ + H+, 495.20899; found (ESI-FTMS, $[M+H]^{1+}$), 495.21035.

Example 8HHHHHHH: N^2-[(3',5'-difluorobiphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0630] MS (ESI) *m/z* 495.2; MS (ESI) *m/z* 989.4; MS (ESI) *m/z* 517.2; HRMS: calcd for $C_{28}H_{28}F_2N_2O_4$ + H+, 495.20899; found (ESI-FTMS, $[M+H]^{1+}$), 495.21017.

Example 8IIIIIII: *N*-[2-(5-chloro-2-thienyl)-1,1-dimethylethyl]-N^2-[(3',4'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine

[0631] MS (ESI) *m/z* 533.3; MS (ESI) *m/z* 1067.7; HRMS: calcd for $C_{26}H_{25}ClF_2N_2O_4S$ + H+, 535.12644; found (ESI-FTMS, $[M+H]^{1+}$), 535.1267.

Example 8JJJJJJJJ: N^2-(biphenyl-4-ylcarbonyl)-*N*-[2-(5-chloro-2-thienyl)-1,1-dimethylethyl]-L-α-glutamine

[0632] MS (ESI) *m/z* 499.4; MS (ESI) *m/z* 997.7; MS (ESI) *m/z* 521.4; HRMS: calcd for $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; found (ESI-FTMS, $[M+H]^{1+}$), 499.14616.

Example 8KKKKKKK: N^2-{[5-(3-chloro-4-fluorophenyl)-2-thienyl]carbonyl}-*N*-[2-(5-chloro-2-thienyl)-1,1-dimethylethyl]-L-α-glutamine

[0633] MS (ESI) *m/z* 557.3; MS (ESI) *m/z* 1113.6; HRMS: calcd for $C_{24}H_{23}Cl_2FN_2O_4S_2$ + H+, 557.05331; found (ESI-FTMS, $[M+H]^{1+}$), 557.05439.

Example 8LLLLLLL: N^2-{[4'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0634] MS (ESI) *m/z* 537.1; MS (ESI) *m/z* 1073.3; HRMS: calcd for $C_{29}H_{32}N_2O_8$ + H+, 537.22314; found (ESI-FTMS, $[M+H]^{1+}$), 537.22326.

Example 8MMMMMMM: N^2-{[4'-(bromomethyl)biphenyl-4-yl]carbonyl}-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0635] MS (ESI) *m/z* 599.1; MS (ESI) *m/z* 1197.1; HRMS: calcd for $C_{29}H_{31}BrN_2O_7$ + H+, 599.13874; found (ESI-FTMS, $[M+H]^{1+}$), 599.13934.

Example 8NNNNNNN: *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[4-(2-thienyl)benzoyl]-L-α-glutamine

[0636] MS (ESI) *m/z* 483.3; MS (ESI) *m/z* 965.5; HRMS: calcd for $C_{26}H_{27}FN_2O_4S$ + H+, 483.17483; found (ESI-FTMS, $[M+H]^{1+}$), 483.1743.

Example 8OOOOOOO: *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[4-(2-furyl)benzoyl]-L-α-glutamine

[0637] MS (ESI) *m/z* 467.3; MS (ESI) *m/z* 933.6; HRMS: calcd for $C_{26}H_{27}FN_2O_5$ + H+, 467.19768; found (ESI-FTMS, $[M+H]^{1+}$), 467.19704.

Example 8PPPPPPP: N^2-{[4'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-*N*-(3-methylbenzyl)-L-α-glutamine

[0638] MS (ESI) *m/z* 459.1; MS (ESI) *m/z* 919.5; HRMS: calcd for $C_{27}H_{28}N_2O_5$ + H+, 461.20710; found (ESI-FTMS, $[M+H]^{1+}$), 461.20822.

Example 8QQQQQQQ: N^2-{[3'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-*N*-(3-methylbenzyl)-L-α-glutamine

[0639] MS (ESI) *m/z* 459.2; HRMS: calcd for $C_{27}H_{28}N_2O_5$ + H+, 461.20710; found (ESI-FTMS, $[M+H]^{1+}$), 461.20807.

Example 8RRRRRRR: N^2-[4-(2,3-dihydro-1-benzofuran-5-yl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0640] MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1035.7; HRMS: calcd for $C_{30}H_{31}FN_2O_5$ + H+, 519.22898; found (ESI-FTMS, $[M+H]^{1+}$), 519.22989.

Example 8SSSSSSS: N^2-[(3'-chloro-4'-fluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0641] MS (ESI) *m/z* 529.3; MS (ESI) *m/z* 1057.6; HRMS: calcd for $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; found (ESI-FTMS, $[M+H]^{1+}$), 529.17061.

Example 8TTTTTTT: N^2-{[3'-(bromomethyl)biphenyl-4-yl]carbonyl}-*N*-(3-methylbenzyl)-L-α-glutamine

[0642] MS (ESI) *m/z* 521.1; HRMS: calcd for $C_{27}H_{27}BrN_2O_4$ + H+, 523.12270; found (ESI-FTMS, $[M+H]^{1+}$), 523.12235.

Example 8UUUUUUU: *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[4-(3-thienyl)benzoyl]-L-α-glutamine

[0643] MS (ESI) *m/z* 483.1; MS (ESI) *m/z* 965.3; HRMS: calcd for $C_{26}H_{27}FN_2O_4S$ + H+, 483.17483; found (ESI-FTMS, $[M+H]^{1+}$), 483.17572.

Example 8VVVVVVV: *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[4-(5-methyl-2-thienyl)benzoyl]-L-α-glutamine

[0644] MS (ESI) *m/z* 495.4; MS (ESI) *m/z* 991.7; HRMS: calcd for $C_{27}H_{29}FN_2O_4S$ + H+, 497.19048; found (ESI-FTMS, $[M+H]^{1+}$), 497.19118.

Example 8WWWWWWW: N^2-[4-(5-chloro-2-thienyl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0645] MS (ESI) *m/z* 515.3; MS (ESI) *m/z* 1031.7; HRMS: calcd for $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; found (ESI-FTMS, $[M+H]^{1+}$), 517.13644.

[0646] MS (ESI) *m/z* 515.3; MS (ESI) *m/z* 1031.6; HRMS: calcd for $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; found (ESI-FTMS, $[M+H]^{1+}$), 517.13658.

Example 8XXXXXXX: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(2-thienyl)benzoyl]-L-α-glutamine

[0647] MS (ESI) *m/z* 497.3; MS (ESI) *m/z* 995.6; HRMS: calcd for $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; found (ESI-FTMS, $[M+H]^{1+}$), 499.14509.

Example 8YYYYYYY: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-{[5-(3-methoxyphenyl)-2-thienyl]carbonyl}-L-α-glutamine

[0648] MS (ESI) *m/z* 529.3; MS (ESI) *m/z* 1057.5; HRMS: calcd for $C_{27}H_{29}ClN_2O_5S$ + H+, 529.15585; found (ESI-FTMS, $[M+H]^{1+}$), 529.15608.

Example 8ZZZZZZZ: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(5-phenyl-2-thienyl)carbonyl]-L-α-glutamine

[0649] MS (ESI) *m/z* 499.2; MS (ESI) *m/z* 997.5; HRMS: calcd for $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; found (ESI-FTMS, $[M+H]^{1+}$), 499.14644.

Example 8AAAAAAAA: N^2-(2,2'-bithien-5-ylcarbonyl)-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0650] MS (ESI) *m/z* 505.1; MS (ESI) *m/z* 1009.1; HRMS: calcd for $C_{24}H_{25}ClN_2O_4S_2$ + H+, 505.10170; found (ESI-FTMS, $[M+H]^{1+}$), 505.10282.

Example 8BBBBBBBB: N^2-[4-(2,3-dihydro-1-benzofuran-6-yl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0651] MS (ESI) *m/z* 517.5; MS (ESI) *m/z* 1035.9; HRMS: calcd for $C_{30}H_{31}FN_2O_5$ + H+, 519.22898; found (ESI-FTMS, $[M+H]^{1+}$), 519.22971.

Example 8CCCCCCCC: *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-{[6-(3-methoxyphenyl)pyridin-3-yl]carbonyl}-L-α-glutamine

[0652] MS (ESI) *m/z* 508.4; HRMS: calcd for $C_{28}H_{30}FN_3O_5$ + H+, 508.22423; found (ESI-FTMS, $[M+H]^{1+}$), 508.22472.

Example 8DDDDDDDD: *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine

[0653] MS (ESI) *m/z* 478.4; HRMS: calcd for $C_{27}H_{28}FN_3O_4$ + H+, 478.21366; found (ESI-FTMS, $[M+H]^{1+}$), 478.21435.

Example 8EEEEEEEE: *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(5-phenyl-2-thienyl)carbonyl]-L-α-glutamine

[0654] MS (ESI) *m/z* 483.2; MS (ESI) *m/z* 965.4; HRMS: calcd for $C_{26}H_{27}FN_2O_4S$ + H+, 483.17483; found (ESI-FTMS, $[M+H]^{1+}$), 483.17576.

Example 8FFFFFFFF: N^2-[(3-fluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0655] MS (ESI) *m/z* 495.3; MS (ESI) *m/z* 989.6; HRMS: calcd for $C_{28}H_{28}F_2N_2O_4$ + H+, 495.20899; found (ESI-FTMS, $[M+H]^{1+}$), 495.20963.

Example 8GGGGGGGG: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(5-pyridin-4-yl-2-thienyl)carbonyl]-L-α-glutamine

[0656] MS (ESI) *m/z* 500.3; HRMS: calcd for $C_{25}H_{26}ClN_3O_4S$ + H+, 500.14053; found (ESI-FTMS, $[M+H]^{1+}$), 500.13984.

Example 8HHHHHHHH: N^2-{[5-(3-chloro-4-fluorophenyl)-2-thienyl]carbonyl}-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0657] MS (ESI) *m/z* 549.3; HRMS: calcd for $C_{26}H_{25}Cl_2FN_2O_4S$ + H+, 551.09689; found (ESI-FTMS, $[M+H]^{1+}$), 551.09834.

Example 8IIIIIII: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(2,3-dihydro-1-benzofuran-6-yl)benzoyl]-L-α-glutamine

[0658] MS (ESI) *m/z* 535.4; MS (ESI) *m/z* 1069.8; HRMS: calcd for $C_{30}H_{31}ClN_2O_5$ + H+, 535.19943; found (ESI-FTMS, $[M+H]^{1+}$), 535.20047.

Example 8JJJJJJJJ: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(5-pyridin-3-yl-2-thienyl)carbonyl]-L-α-glutamine

[0659] MS (ESI) *m/z* 500.3; HRMS: calcd for $C_{25}H_{26}ClN_3O_4S$ + H+, 500.14053; found (ESI-FTMS, $[M+H]^{1+}$), 500.1423.

Example 8KKKKKKKK: N^2-[4-(2,3-dihydro-1-benzofuran-6-yl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0660] MS (ESI) *m/z* 501.4; MS (ESI) *m/z* 1001.8; HRMS: calcd for $C_{30}H_{32}N_2O_5$ + H+, 501.23840; found (ESI-FTMS, $[M+H]^{1+}$), 501.23954.

Example 8LLLLLLLL: N^2-{[5-(3-chloro-4-fluorophenyl)-2-thienyl]carbonyl}-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0661] MS (ESI) *m/z* 515.3; MS (ESI) *m/z* 1031.7; HRMS: calcd for $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; found (ESI-FTMS, $[M+H]^{1+}$), 517.13443.

Example 8MMMMMMMM: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[4-(2-thienyl)benzoyl]-L-α-glutamine

[0662] MS (ESI) *m/z* 465.2; MS (ESI) *m/z* 929.4; HRMS: calcd for $C_{26}H_{28}N_2O_4S$ + H+, 465.18425; found (ESI-FTMS, $[M+H]^{1+}$), 465.18402.

Example 8NNNNNNNN: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-{[5-(3-methoxyphenyl)-2-thienyl]carbonyl}-L-α-glutamine

[0663] MS (ESI) *m/z* 495.2; MS (ESI) *m/z* 989.4; HRMS: calcd for $C_{27}H_{30}N_2O_5S$ + H+, 495.19482; found (ESI-FTMS, $[M+H]^{1+}$), 495.1942.

Example 8OOOOOOOO: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(5-phenyl-2-thienyl)carbonyl]-L-α-glutamine

[0664] MS (ESI) *m/z* 465.2; MS (ESI) *m/z* 929.4; HRMS: calcd for $C_{26}H_{28}N_2O_4S$ + H+, 465.18425; found (ESI-FTMS, $[M+H]^{1+}$), 465.18359.

Example 8PPPPPPPP: N^2-(2,2'-bithien-5-ylcarbonyl)-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0665] MS (ESI) *m/z* 469.3; MS (ESI) *m/z* 939.6; HRMS: calcd for $C_{24}H_{26}N_2O_4S_2$ + H+, 471.14067; found (ESI-FTMS, $[M+H]^{1+}$), 471.1403.

Example 8QQQQQQQQ: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(5-pyridin-4-yl-2-thienyl)carbonyl]-L-α-glutamine

[0666] MS (ESI) *m/z* 466.4; HRMS: calcd for $C_{25}H_{27}N_3O_4S$ + H+, 466.17950; found (ESI-FTMS, $[M+H]^{1+}$), 466.17836.

Example 8RRRRRRRR: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(5-pyridin-3-yl-2-thienyl)carbonyl]-L-α-glutamine

[0667] MS (ESI) *m/z* 466.3; HRMS: calcd for $C_{25}H_{27}N_3O_4S$ + H+, 466.17950; found (ESI-FTMS, $[M+H]^{1+}$), 466.17912.

Example 8SSSSSSSS: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(5-chloro-2-thienyl)benzoyl]-L-α-glutamine

[0668] HRMS: calcd for $C_{26}H_{26}Cl_2N_2O_4S$ + H+, 533.10631; found (ESI-FTMS, $[M+H]^{1+}$), 533.10629.

Example 8TTTTTTTT: N^2-{[6-(5-chloro-2-thienyl)pyridin-3-yl]carbonyl}-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0669] MS (ESI) *m/z* 500.3; MS (ESI) *m/z* 999.6; HRMS: calcd for $C_{25}H_{26}ClN_3O_4S$ + H+, 500.14053; found (ESI-FTMS, $[M+H]^{1+}$), 500.14123.

Example 8UUUUUUUU: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine

[0670] MS (ESI) *m/z* 460.4; HRMS: calcd for $C_{27}H_{29}N_3O_4$ + H+, 460.22308; found (ESI-FTMS, $[M+H]^{1+}$), 460.22319.

Example 8VVVVVVVV: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-(5-phenyl-2-furoyl)-L-α-glutamine

[0671] MS (ESI) *m/z* 483.3; MS (ESI) *m/z* 965.6; MS (ESI) *m/z* 987.6; HRMS: calcd for $C_{26}H_{27}ClN_2O_5$ + H+, 483.16813; found (ESI-FTMS, $[M+H]^{1+}$), 483.16818.

Example 8WWWWWWWW: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-{[6-(5-chloro-2-thienyl)pyridin-3-yl]carbonyl}-L-α-glutamine

[0672] MS (ESI) *m/z* 534.3; HRMS: calcd for $C_{25}H_{25}Cl_2N_3O_4S$ + H+, 534.10156; found (ESI-FTMS, $[M+H]^{1+}$), 534.10123.

Example 8XXXXXXXX: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine

[0673] MS (ESI) *m/z* 494.4; HRMS: calcd for $C_{27}H_{28}ClN_3O_4$ + H+, 494.18411; found (ESI-FTMS, $[M+H]^{1+}$), 494.18423.

Example 8YYYYYYYY: *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-{[5-(3-methoxyphenyl)-2-thienyl]carbonyl}-L-α-glutamine

[0674] MS (ESI) *m/z* 513.3; MS (ESI) *m/z* 1025.7; HRMS: calcd for $C_{27}H_{29}FN_2O_5S$ + H+, 513.18540; found (ESI-FTMS, $[M+H]^{1+}$), 513.18635.

Example 8ZZZZZZZZ: *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(5-pyridin-3-yl-2-thienyl)carbonyl]-L-α-glutamine

[0675] MS (ESI) *m/z* 484.3; HRMS: calcd for $C_{25}H_{26}FN_3O_4S$ + H+, 484.17008; found (ESI-FTMS, $[M+H]^{1+}$), 484.17109.

Example 8AAAAAAAAA: N^2-{[5-(3-chloro-4-fluorophenyl)-2-thienyl]carbonyl}-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0676] MS (ESI) *m/z* 535.2; MS (ESI) *m/z* 557.2; MS (ESI) *m/z* 1069.5; HRMS: calcd for $C_{26}H_{25}ClF_2N_2O_4S$ + H+, 535.12644; found (ESI-FTMS, $[M+H]^{1+}$), 535.12696.

[0677] MS (ESI) *m/z* 533.3; MS (ESI) *m/z* 1067.6; HRMS: calcd for $C_{26}H_{25}ClF_2N_2O_4S$ + H+, 535.12644; found (ESI-FTMS, $[M+H]^{1+}$), 535.12796.

Example 8BBBBBBBBB: N^2-(2,2'-bithien-5-ylcarbonyl)-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0678] MS (ESI) *m/z* 489.3; MS (ESI) *m/z* 977.5; HRMS: calcd for $C_{24}H_{25}FN_2O_4S_2$ + H+, 489.13125; found (ESI-FTMS, $[M+H]^{1+}$), 489.13208.

Example 8CCCCCCCCC: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(5-formyl-2-thienyl)benzoyl]-L-α-glutamine

[0679] MS (ESI) *m/z* 527.1; MS (ESI) *m/z* 1053.1; MS (ESI) *m/z* 549; HRMS: calcd for $C_{27}H_{27}ClN_2O_5S$ + H+, 527.14020; found (ESI-FTMS, $[M+H]^{1+}$), 527.14185.

Example 8DDDDDDDDD: N^2-[4-(5-acetyl-2-thienyl)benzoyl]-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0680] MS (ESI) *m/z* 541.1; MS (ESI) *m/z* 1081.2; MS (ESI) *m/z* 563.1; HRMS: calcd for $C_{28}H_{29}ClN_2O_5S$ + H+, 541.15585; found (ESI-FTMS, $[M+H]^{1+}$), 541.15471.

Example 8EEEEEEEEE: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(1,3-thiazol-2-yl)benzoyl]-L-α-glutamine

[0681] MS (ESI) *m/z* 500.3; HRMS: calcd for $C_{25}H_{26}ClN_3O_4S$ + H+, 500.14053; found (ESI-FTMS, $[M+H]^{1+}$), 500.14163.

Example 8FFFFFFFFF: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[4-(1,3-thiazol-2-yl)benzoyl]-L-α-glutamine

[0682] MS (ESI) *m/z* 466.3; HRMS: calcd for $C_{25}H_{27}N_3O_4S$ + H+, 466.17950; found (ESI-FTMS, $[M+H]^{1+}$), 466.18052.

Example 8GGGGGGGGG: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-(5-phenyl-2-furoyl)-L-α-glutamine

[0683] MS (ESI) *m/z* 449.3; MS (ESI) *m/z* 897.6; MS (ESI) *m/z* 471.3; HRMS: calcd for $C_{26}H_{28}N_2O_5$ + H+, 449.20710; found (ESI-FTMS, $[M+H]^{1+}$), 449.20772.

Example 8HHHHHHHHH: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[4-(5-formyl-2-thienyl)benzoyl]-L-α-glutamine

[0684] MS (ESI) *m/z* 493.3; MS (ESI) *m/z* 985.6; MS (ESI) *m/z* 515.3; HRMS: calcd for $C_{27}H_{28}N_2O_5S$ + H+, 493.17917; found (ESI-FTMS, $[M+H]^{1+}$), 493.18011.

Example 8IIIIIIII: N^2-[4-(5-acetyl-2-thienyl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0685] MS (ESI) *m/z* 507.3; MS (ESI) *m/z* 1013.7; MS (ESI) *m/z* 529.3; HRMS: calcd for $C_{28}H_{30}N_2O_5S$ + H+, 507.19482; found (ESI-FTMS, $[M+H]^{1+}$), 507.19518.

Example 8JJJJJJJJJ: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[3-(5-chloro-2-thienyl)benzoyl]-L-α-glutamine

[0686] MS (ESI) *m/z* 533.3; MS (ESI) *m/z* 1065.5; MS (ESI) *m/z* 555.3; HRMS: calcd for $C_{26}H_{26}Cl_2N_2O_4S$ + H+, 533.10631; found (ESI-FTMS, $[M+H]^{1+}$), 533.10835.

Example 8KKKKKKKKK: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[3-(2-thienyl)benzoyl]-L-α-glutamine

[0687] MS (ESI) *m/z* 499.3; MS (ESI) *m/z* 997.6; MS (ESI) *m/z* 521.3; HRMS: calcd for $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; found (ESI-FTMS, $[M+H]^{1+}$), 499.14679.

Example 8LLLLLLLLL: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-{[5-(4-chlorophenyl)-2-thienyl]carbonyl}-L-α-glutamine

[0688] MS (ESI) *m/z* 533.3; MS (ESI) *m/z* 1065.5; MS (ESI) *m/z* 555.3; HRMS: calcd for $C_{26}H_{26}Cl_2N_2O_4S$ + H+, 533.10631; found (ESI-FTMS, $[M+H]^{1+}$), 533.10784.

Example 8MMMMMMMMM: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-{[5-(4-fluorophenyl)-2-thienyl]carbonyl}-L-α-glutamine

[0689] MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 539.3; MS (ESI) *m/z* 1033.6; HRMS: calcd for $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; found (ESI-FTMS, $[M+H]^{1+}$), 517.13691.

Example 8NNNNNNNNN: N^2-[4-(5-bromo-2-thienyl)benzoyl]-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0690] MS (ESI) *m/z* 577.2; MS (ESI) *m/z* 1153.4; HRMS: calcd for $C_{26}H_{26}BrClN_2O_4S$ + H+, 577.05579; found (ESI-FTMS, $[M+H]^{1+}$), 577.05597.

Example 8OOOOOOOOO: N^2-[4-(5-bromo-2-thienyl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0691] MS (ESI) *m/z* 543.1; MS (ESI) *m/z* 1085.2; HRMS: calcd for $C_{26}H_{27}BrN_2O_4S$ + H+, 543.09477; found (ESI-FTMS, $[M+H]^{1+}$), 543.0965; HRMS: calcd for $C_{26}H_{27}BrN_2O_4S$ + H+, 543.09477; found (ESI-FTMS, $[M+H]^{1+}$), 543.09494.

Example 8PPPPPPPPP: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-{[5-(4-fluorophenyl)-2-thienyl]carbonyl}-L-α-glutamine

[0692] MS (ESI) *m/z* 483.2; MS (ESI) *m/z* 965.4; MS (ESI) *m/z* 505.2; HRMS: calcd for $C_{26}H_{27}FN_2O_4S$ + H+, 483.17483; found (ESI-FTMS, $[M+H]^{1+}$), 483.17634.

Example 8QQQQQQQQQ: N^2-[3-(5-chloro-2-thienyl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0693] MS (ESI) *m/z* 499.2; MS (ESI) *m/z* 997.3; MS (ESI) *m/z* 521.1; HRMS: calcd for $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; found (ESI-FTMS, $[M+H]^{1+}$), 499.14544.

Example 8RRRRRRRRR: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[3-(2-thienyl)benzoyl]-L-α-glutamine

[0694] MS (ESI) *m/z* 465.2; MS (ESI) *m/z* 929.4; MS (ESI) *m/z* 487.2; HRMS: calcd for $C_{26}H_{28}N_2O_4S$ + H+, 465.18425; found (ESI-FTMS, $[M+H]^{1+}$), 465.18439.

Example 8SSSSSSSSS: N^2-[(3'-chlorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0695] HRMS: calcd for $C_{28}H_{28}ClFN_2O_4$ + H+, 511.17944; found (ESI-FTMS, $[M+H]^{1+}$), 511.17974.

Example 8TTTTTTTTT: N^2-[(4'-chlorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0696] HRMS: calcd for $C_{28}H_{28}ClFN_2O_4$ + H+, 511.17944; found (ESI-FTMS, $[M+H]^{1+}$), 511.17972.

Example 8UUUUUUUUU: N^2-[(4'-fluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0697] HRMS: calcd for $C_{28}H_{28}F_2N_2O_4$ + H+, 495.20899; found (ESI-FTMS, $[M+H]^{1+}$), 495.20933.

Example 8VVVVVVVVV: N^2-[(3'-fluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0698] HRMS: calcd for $C_{28}H_{28}F_2N_2O_4$ + H+, 495.20899; found (ESI-FTMS, $[M+H]^{1+}$), 495.20937.

Example 8WWWWWWWWW: *N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(3-phenyl-2-thienyl)carbonyl]-L-α-glutamine

[0699] HRMS: calcd for $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; found (ESI-FTMS, $[M+H]^{1+}$), 499.14664.

Example 8XXXXXXXXX: N^2-[(4'-chlorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0700] MS (ESI) *m/z* 527.3; MS (ESI) *m/z* 1053.7; MS (ESI) *m/z* 549.3; HRMS: calcd for $C_{28}H_{28}Cl_2N_2O_4$ + H+, 527.14989; found (ESI-FTMS, $[M+H]^{1+}$), 527.15049.

[0701] HRMS: calcd for $C_{28}H_{28}Cl_2N_2O_4$ + H+, 527.14989; found (ESI-FTMS, $[M+H]^{1+}$), 527.14931.

Example 8YYYYYYYYY: N^2-[(3'-chlorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0702] MS (ESI) *m/z* 527.3; MS (ESI) *m/z* 1053.7; MS (ESI) *m/z* 549.3; HRMS: calcd for $C_{28}H_{28}Cl_2N_2O_4$ + H+, 527.14989; found (ESI-FTMS, $[M+H]^{1+}$), 527.15048.

Example 8ZZZZZZZZZ: *N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-{[5-(4-fluorophenyl)-2-thienyl]carbonyl}-L-α-glutamine

[0703] MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.6; MS (ESI) *m/z* 523.3; HRMS: calcd for $C_{26}H_{26}F_2N_2O_4S$ + H+, 501.16541; found (ESI-FTMS, $[M+H]^{1+}$), 501.16642.

[0704] MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.6; MS (ESI) *m/z* 523.3; HRMS: calcd for $C_{26}H_{26}F_2N_2O_4S$ + H+, 501.16541; found (ESI-FTMS, $[M+H]^{1+}$), 501.16709.

Example 8AAAAAAAAAA: N^2-{[5-(4-chlorophenyl)-2-thienyl]carbonyl}-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0705] MS (ESI) *m/z* 499.1; MS (ESI) *m/z* 997.2; HRMS: calcd for $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; found (ESI-FTMS, $[M+H]^{1+}$), 499.14552.

Example 8BBBBBBBBBB: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(3-phenyl-2-thienyl)carbonyl]-L-α-glutamine

[0706] MS (ESI) *m/z* 465.2; MS (ESI) *m/z* 929.4; MS (ESI) *m/z* 951.4; HRMS: calcd for $C_{26}H_{28}N_2O_4S$ + H+, 465.18425; found (ESI-FTMS, $[M+H]^{1+}$), 465.18455.

Example 8CCCCCCCCCC: N^2-(4-bromobenzoyl)-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0707] MS (ESI) *m/z* 479.3; MS (ESI) *m/z* 957.5; MS (ESI) *m/z* 501.2; HRMS: calcd for $C_{22}H_{24}BrFN_2O_4$ + H+, 479.09762; found (ESI-FTMS, $[M+H]^{1+}$), 479.0983.

Example 8DDDDDDDDDD: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-fluorobiphenyl-4-yl)carbonyl]-L-α-glutamine

[0708] MS (ESI) *m/z* 477.3; MS (ESI) *m/z* 499.3; MS (ESI) *m/z* 953.7; HRMS: calcd for $C_{28}H_{29}FN_2O_4$ + H+, 477.21841; found (ESI-FTMS, $[M+H]^{1+}$), 477.21891.

Example 8EEEEEEEEEE: *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(3'-fluorobiphenyl-4-yl)carbonyl]-L-α-glutamine

[0709] MS (ESI) *m/z* 477.3; MS (ESI) *m/z* 499.3; MS (ESI) *m/z* 953.7; HRMS: calcd for $C_{28}H_{29}FN_2O_4$ + H+, 477.21841; found (ESI-FTMS, $[M+H]^{1+}$), 477.21875.

Example 8FFFFFFFFFF: N^2-[4-(5-chloro-2-thienyl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-D-α-glutamine

[0710] MS (ESI) *m/z* 517.2; MS (ESI) *m/z* 539.2; MS (ESI) *m/z* 1033.5; HRMS: calcd for $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; found (ESI-FTMS, $[M+H]^{1+}$), 517.1365.

Example 8GGGGGGGGGG: N^2-{[6-(5-chloro-2-thienyl)pyridin-3-yl]carbonyl}-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0711] MS (ESI) *m/z* 518.2; HRMS: calcd for $C_{25}H_{25}ClFN_3O_4S$ + H+, 518.13111; found (ESI-FTMS, $[M+H]^{1+}$), 518.13169.

Example 8HHHHHHHHHH: N^2-{[5-(4-chlorophenyl)-2-thienyl]carbonyl}-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

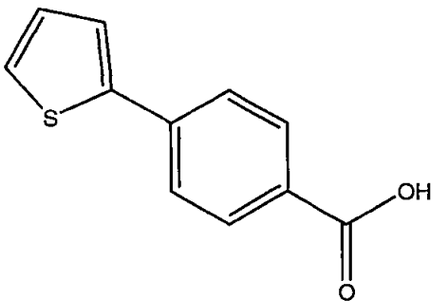
[0712] MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 539.3; MS (ESI) *m/z* 1033.6; HRMS: calcd for $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; found (ESI-FTMS, $[M+H]^{1+}$), 517.1363.

Example 8IIIIIIIII: N^2-{[5-(3,4-difluorophenyl)-2-thienyl]carbonyl}-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0713] MS (ESI) *m/z* 519.3; MS (ESI) *m/z* 1037.7; MS (ESI) *m/z* 541.3; HRMS: calcd for $C_{26}H_{25}F_3N_2O_4S$ + H+, 519.15599; found (ESI-FTMS, $[M+H]^{1+}$), 519.1568.

[0714] The following intermediates (R_1COOH in scheme 7) were prepared and used in the preparation of some of the compounds of Example 8:

Example 8JJJJJJJJJJ: 4-(2-thienyl)benzoic acid



[0715] 4-iodobenzoic acid (3g, 12.1mmol), 2-thiopheneboronic acid (3.10g, 24.2mmol), and $Pd(PPh_3)_4$ (1.4g, 1.21mmol) were dissolved in DMF (75mL) in a 350mL screw-cap pressure vessel. In a separate flask, K_2CO_3 (5.02g, 36.3mmol) was dissolved in H_2O (12mL) and was then added to the reaction. The flask was sealed, heated to 100°C and stirred overnight (17h).

[0716] The reaction was then diluted with H_2O (150mL), placed in a sep. funnel, and 1N NaOH was added to raise the pH to 10. The aqueous layer was washed with EtOAc (2x250mL). The aqueous layer was kept, activated charcoal was added, and the mixture heated and stirred. Celite was added, followed by the mixture being filtered through celite. The filtrate was then acidified with concentrated HCl. At pH 7 a tan solid starts to precipitate. The pH was lowered to 5 and the solid formed is filtered out. The solid was partially dissolved in a small amount of toluene, which was then removed to remove some of the water still present. This step was repeated, then the solid was dried under vacuum. Yield – 2.01g tan solid, 81%. MS (ESI) *m/z* 202.9; HRMS: calcd for $C_{11}H_8O_2S$ + H+, 205.03178; found (ESI-FTMS, $[M+H]^{1+}$), 205.03127.

[0717] The following compounds were prepared according to the procedure similar to the one described in Example 8JJJJJJJJJJ, from appropriate commercially available reagents:

i: 5-(3-methoxyphenyl)thiophene-2-carboxylic acid

MS (ESI) *m/z* 233.1; HRMS: calcd for $C_{12}H_{10}O_3S$ + H+, 235.04234; found (ESI-FTMS, $[M+H]^{1+}$), 235.04226;

ii. 2,2'-bithiophene-5-carboxylic acid

MS (ESI) *m/z* 209.1; HRMS: calcd for $C_9H_6O_2S_2$ + H+, 210.98820; found (ESI-FTMS, $[M+H]^{1+}$), 210.98816;

iii. 5-pyridin-4-ylthiophene-2-carboxylic acid

MS (ESI) *m/z* 206.1; HRMS: calcd for $C_{10}H_7NO_2S$ + H+, 206.02703; found (ESI-FTMS, $[M+H]^{1+}$), 206.02691;

iv. 4-(5-chloro-2-thienyl)benzoic acid

HRMS: calcd for $C_{11}H_7ClO_2S$ - H+, 236.97825; found (ESI-FTMS, $[M-H]^{1-}$), 236.97751;

v. 5-phenyl-2-furoic acid

HRMS: calcd for $C_{11}H_8O_3$ + H+, 189.05462; found (ESI-FTMS, $[M+H]^{1+}$), 189.05445;

vi. 4-(5-acetyl-2-thienyl)benzoic acid

MS (ESI) *m/z* 245.1; HRMS: calcd for $C_{13}H_{10}O_3S$ + H+, 247.04234; found (ESI-FTMS, $[M+H]^{1+}$), 247.04223;

vii. 3-(5-chloro-2-thienyl)benzoic acid

MS (ESI) *m/z* 237; HRMS: calcd for $C_{11}H_7ClO_2S$ - H+, 236.97825; found (ESI-FTMS, $[M-H]^{1-}$), 236.97757;

viii. 3-(2-thienyl)benzoic acid

MS (ESI) *m/z* 203.1; HRMS: calcd for $C_{11}H_8O_2S$ + H+, 205.03178; found (ESI-FTMS, $[M+H]^{1+}$), 205.03194;

ix. 5-(4-chlorophenyl)thiophene-2-carboxylic acid

MS (ESI) *m/z* 237; MS (ESI) *m/z* 283; MS (ESI) *m/z* 475.1; HRMS: calcd for $C_{11}H_7ClO_2S$ - H+, 236.97825; found (ESI-FTMS, $[M-H]^{1-}$), 236.97825;

x. 3-phenylthiophene-2-carboxylic acid

MS (ESI) *m/z* 203.1; MS (ESI) *m/z* 249.1; HRMS: calcd for $C_{11}H_8O_2S$ + H+, 205.03178; found (ESI-FTMS, $[M+H]^{1+}$), 205.03177;

xi. 4'-chlorobiphenyl-4-carboxylic acid

MS (ESI) *m/z* 231.1; HRMS: calcd for $C_{13}H_9ClO_2$ - H+, 231.02183; found (ESI-FTMS,
$[M-H]^{1-}$), 231.02129;

xii. 3'-chlorobiphenyl-4-carboxylic acid

MS (ESI) *m/z* 231.1; HRMS: calcd for $C_{13}H_9ClO_2$ - H+, 231.02183; found (ESI-FTMS,
$[M-H]^{1-}$), 231.02128;

xiii. 5-(3,4-difluorophenyl)thiophene-2-carboxylic acid

MS (ESI) *m/z* 239; MS (ESI) *m/z* 285.1; MS (ESI) *m/z* 479.1; HRMS: calcd for $C_{11}H_6F_2O_2S$ + H+, 241.01293; found (ESI-FTMS, $[M+H]^{1+}$), 241.01183;

xiv. 5-(2,4-difluorophenyl)thiophene-2-carboxylic acid

MS (ESI) *m/z* 239; MS (ESI) *m/z* 285; HRMS: calcd for $C_{11}H_6F_2O_2S$ + H+, 241.01293; found (ESI-FTMS, $[M+H]^{1+}$), 241.01187;

xv. 4-phenoxybenzoic acid

MS (ESI) *m/z* 213.1; HRMS: calcd for $C_{13}H_{10}O_3$ + H+, 215.07027; found (ESI-FTMS, $[M+H]^{1+}$), 215.07029;

xvi. 4-(2,3-dihydro-1-benzofuran-6-yl)benzoic acid

MS (ESI) *m/z* 239.1; HRMS: calcd for $C_{15}H_{12}O_3$ - H+, 239.07137; found (ESI-FTMS, $[M-H]^{1-}$), 239.07131;

xvii. 5-(3-chloro-4-fluorophenyl)thiophene-2-carboxylic acid

MS (ESI) *m/z* 255.1; MS (ESI) *m/z* 511.2; HRMS: calcd for $C_{11}H_6ClFO_2S$ - H+, 254.96883; found (ESI-FTMS, $[M-H]^{1-}$), 254.96892;

xviii. 5-pyridin-3-ylthiophene-2-carboxylic acid

MS (ESI) *m/z* 206.1; HRMS: calcd for $C_{10}H_7NO_2S$ + H+, 206.02703; found (ESI-FTMS, $[M+H]^{1+}$), 206.02708;

xix. 6-(5-chloro-2-thienyl)nicotinic acid

MS (ESI) *m/z* 238;

xx. 6-phenylnicotinic acid

MS (ESI) *m/z* 200.1; HRMS: calcd for $C_{12}H_9NO_2$ + H+, 200.07061; found (ESI-FTMS, $[M+H]^{1+}$), 200.07052;

xxi. 4-(1,3-thiazol-2-yl)benzoic acid

mp 235 - 237 °C; MS (ESI) *m/z* 206; MS (ESI) *m/z* 204;

xxii. 4-(5-bromo-2-thienyl)benzoic acid

MS (ESI) *m/z* 281; MS (ESI) *m/z* 394.8;

xxiii. 5-(4-fluorophenyl)thiophene-2-carboxylic acid

MS (ES) *m/z* 221.0; MS (ES) *m/z* 443.0;

xxiv. 4-[5-(aminosulfonyl)-2-thienyl]benzoic acid

MS (ESI) *m/z* 282.1; MS (ESI) *m/z* 565.2;

xxv. 4-(5-cyano-2-thienyl)benzoic acid

MS (ESI) *m/z* 228.1;

xxvi. 3'-fluorobiphenyl-4-carboxylic acid

MS (ESI) *m/z* 215.1;

xxvii. 3',4'-difluorobiphenyl-4-carboxylic acid

MS (ESI) *m/z* 233;

xxviii. 2',4'-difluorobiphenyl-4-carboxylic acid

MS (ESI) *m/z* 233.1;

xxix. 2',5'-difluorobiphenyl-4-carboxylic acid

MS (ESI) *m/z* 233.1;

xxx. 3',5'-difluorobiphenyl-4-carboxylic acid

MS (ESI) *m/z* 233.1;

xxxi. 2',6'-difluorobiphenyl-4-carboxylic acid

MS (ESI) *m/z* 233.1;

xxxii. 2',3'-difluorobiphenyl-4-carboxylic acid

MS (ESI) *m/z* 233;

xxxiii. 4-(5-methyl-2-thienyl)benzoic acid

MS (ESI) *m/z* 217.1; HRMS: calcd for $C_{12}H_{10}O_2S$ + H+, 219.04743; found (ESI-FTMS, $[M+H]^{1+}$), 219.04744;

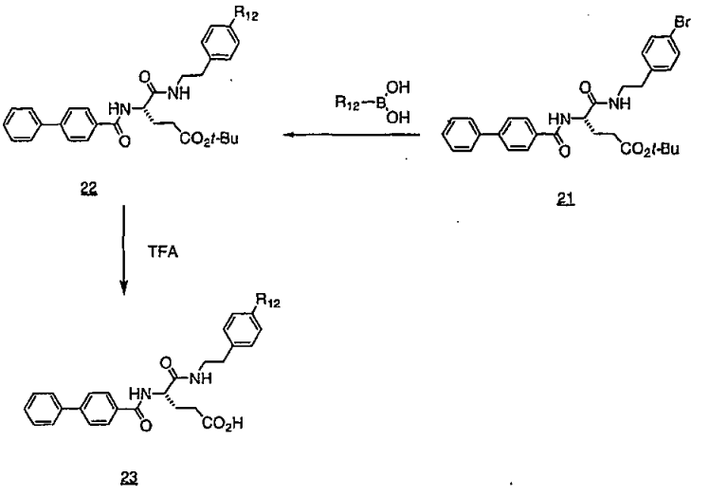
xxxiv. 6-(3-methoxyphenyl)nicotinic acid

MS (ESI) *m/z* 230.1;

xxxv. 3-fluorobiphenyl-4-carboxylic acid

MS (ESI) *m/z* 215.1; HRMS: calcd for $C_{13}H_9FO_2$ + H+, 217.06593; found (ESI-FTMS, $[M+H]^{1+}$), 217.06598.

Scheme 8



Example 9: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-4-yl)ethyl]-L-α-glutamine

[0718] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-4-yl)ethyl]-L-α-glutaminate

tert-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-bromophenyl)ethyl]-L-α-glutaminate (333 mg, 0.59 mmol, 1 equiv.) was dissolved in DME (5 mL) and the mixture was added to 4-formylphenyl boronic acid (0.97 g, 0.65 mmol, 1.1 equiv.) and $Pd(PPh_3)_4$ (68 mg, 0.059 mmol, 0.1 equiv.) and stirred for 30 minutes prior to the addition of aq. K_2CO_3 (163 mg, 1.18 mmol, 2 equiv.) in 1 mL H_2O. The mixture was capped in a sealed vessel and stirred overnight at 80°C. The reaction was complete as determined by TLC. The mixture was filtered over celite, the solvent was removed, and the resulting tan solid was diluted with EtOAc (20 mL) and washed consecutively with H_2O, 10% HCl, brine, and dried over Na_2SO_4. The solid was purified by column chromatography (silica gel, 41% Acetone/Hexanes) to give 38 mg of *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-4-yl)ethyl]-L-α-glutaminate in 11% yield.

MS (ESI) *m/z* 591.3; MS (ESI) *m/z* 1181.5; HRMS: calcd for $C_{37}H_{38}N_2O_5$ + H+, 591.28535; found (ESI-FTMS, $[M+H]^{1+}$), 591.28473.

[0719] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-4-yl)ethyl]-L-α-glutamine

tert-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-4-yl)ethyl]-L-α-glutaminate (100 mg, 0.17 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (5 mL) and added to TFA (2 mL). The mixture was stirred at room temperature for 3 hrs. The reaction was complete as determined by TLC. Solvent was removed and the resulting solid was purified by preparative HPLC to give N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-4-yl)ethyl]-L-α-glutamine in 89% yield (80 mg). MS (ESI) *m/z* 533.1; HRMS: calcd for $C_{33}H_{30}N_2O_5$ + H+, 535.22275; found (ESI-FTMS, $[M+H]^{1+}$), 535.22464.

Example 10:

[0720] The following compounds were prepared according to procedures similar to those described in Example 9.

Example 10A: N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4'-(trifluoromethyl)biphenyl-4-yl]ethyl}-L-α-glutamine

[0721] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4'-(trifluoromethyl)biphenyl-4-yl]ethyl}-L-α-glutaminate

MS (ESI) *m/z* 631.2; MS (ESI) *m/z* 1261.4; MS (ESI) *m/z* 653.2; HRMS: calcd for $C_{37}H_{37}F_3N_2O_4$ + H+, 631.27782; found (ESI-FTMS, $[M+H]^{1+}$), 631.27719.

[0722] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4'-(trifluoromethyl)biphenyl-4-yl]ethyl}-L-α-glutamine

HRMS: calcd for $C_{33}H_{29}F_3N_2O_4$ + H+, 575.21522; found (ESI-FTMS, $[M+H]^{1+}$), 575.21548.

Example 10B: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-methoxybiphenyl-4-yl)ethyl]-L-α-glutamine

[0723] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-methoxybiphenyl-4-yl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 593.3; MS (ESI) *m/z* 1185.5; HRMS: calcd for $C_{37}H_{40}N_2O_5$ + H+, 593.30100; found (ESI-FTMS, $[M+H]^{1+}$), 593.29946.

[0724] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-methoxybiphenyl-4-yl)ethyl]-L-α-glutamine

HRMS: calcd for $C_{33}H_{32}N_2O_5$ + H+, 537.23840; found (ESI-FTMS, $[M+H]^{1+}$), 537.23906.

Example 10C: N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-biphenyl-4-ylethyl)-L-α-glutamine

[0725] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-biphenyl-4-ylethyl)-L-α-glutaminate

MS (ESI) *m/z* 563.3; MS (ESI) *m/z* 1125.5; HRMS: calcd for $C_{36}H_{38}N_2O_4$ + H+, 563.29043; found (ESI-FTMS, $[M+H]^{1+}$), 563.28977.

[0726] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-biphenyl-4-ylethyl)-L-α-glutamine

HRMS: calcd for $C_{32}H_{30}N_2O_4$ + H+, 507.22783; found (ESI-FTMS, $[M+H]^{1+}$), 507.22688.

Example 10D: N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4-(2-thienyl)phenyl]ethyl}-L-α-glutamine

[0727] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4-(2-thienyl)phenyl]ethyl}-L-α-glutaminate

MS (ESI) *m/z* 569.2; MS (ESI) *m/z* 1137.4; HRMS: calcd for $C_{34}H_{36}N_2O_4S$ + H+, 569.24685; found (ESI-FTMS, $[M+H]^{1+}$), 569.24702.

[0728] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4-(2-thienyl)phenyl]ethyl}-L-α-glutamine

MS (ESI) *m/z* 511.1; HRMS: calcd for $C_{30}H_{28}N_2O_4S$ + H+, 513.18425; found (ESI-FTMS, $[M+H]^{1+}$), 513.18417.

Example 10E: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2'-ethoxybiphenyl-4-yl)ethyl]-L-α-glutamine

[0729] MS (ESI) *m/z* 551.1; MS (ESI) *m/z* 1101.4; MS (ESI) *m/z* 573.1; HRMS: calcd for $C_{34}H_{34}N_2O_5$ + H+, 551.25405; found (ESI-FTMS, $[M+H]^{1+}$), 551.2538.

Example 10F: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-ethynylbiphenyl-4-yl)ethyl]-L-α-glutamine

[0730] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-ethynylbiphenyl-4-yl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 587.3; MS (ESI) *m/z* 1173.5; HRMS: calcd for $C_{38}H_{38}N_2O_4$ + H+, 587.29043; found (ESI-FTMS, $[M+H]^{1+}$), 587.29016.

[0731] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-ethynylbiphenyl-4-yl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 529.2; HRMS: calcd for $C_{34}H_{30}N_2O_4$ + H+, 531.22783; found (ESI-FTMS, $[M+H]^{1+}$), 531.22669.

Example 10G: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-pyridin-2-ylphenyl)ethyl]-L-α-glutamine

[0732] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-pyridin-2-ylphenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 564.3; HRMS: calcd for $C_{35}H_{37}N_3O_4$ + H+, 564.28568; found (ESI-FTMS, $[M+H]^{1+}$), 564.28472.

[0733] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-pyridin-2-ylphenyl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 508.2.

Example 10H: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-pyridin-4-ylphenyl)ethyl]-L-α-glutamine

[0734] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-pyridin-4-ylphenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 564.2; HRMS: calcd for $C_{35}H_{37}N_3O_4$ + H+, 564.28568; found (ESI-FTMS, $[M+H]^{1+}$), 564.28648.

[0735] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-pyridin-4-ylphenyl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 508.1; MS (ESI) *m/z* 275.1; HRMS: calcd for $C_{31}H_{29}N_3O_4$ + H+, 508.22308; found (ESI-FTMS, $[M+H]^{1+}$), 508.22403.

Example 10I: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(3-pyridin-2-ylphenyl)ethyl]-L-α-glutamine

[0736] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(3-pyridin-2-ylphenyl)ethyl]-L-α-glutaminate

MS (ESI) *m/z* 564.3; HRMS: calcd for $C_{35}H_{37}N_3O_4$ + H+, 564.28568; found (ESI-FTMS, $[M+H]^{1+}$), 564.28531.

[0737] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(3-pyridin-2-ylphenyl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 508.1; HRMS: calcd for $C_{31}H_{29}N_3O_4$ + H+, 508.22308; found (ESI-FTMS, $[M+H]^{1+}$), 508.22432.

Example 10J: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-3-yl)ethyl]-L-α-glutamine

[0738] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-3-yl)ethyl]-L-α-glutaminate

[0739] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-3-yl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 535.2; MS (ESI) *m/z* 1069.3; HRMS: calcd for $C_{33}H_{30}N_2O_5$ + H+, 535.22275; found (ESI-FTMS, $[M+H]^{1+}$), 535.22147.

Example 10K: N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4'-(trifluoromethyl)biphenyl-3-yl]ethyl}-L-α-glutamine

[0740] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4'-(trifluoromethyl)biphenyl-3-yl]ethyl}-L-α-glutaminate

HRMS: calcd for $C_{37}H_{37}F_3N_2O_4$ + H+, 631.27782; found (ESI-FTMS, $[M+H]^{1+}$), 631.27639.

[0741] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4'-(trifluoromethyl)biphenyl-3-yl]ethyl}-L-α-glutamine

MS (ESI) *m/z* 575.2; HRMS: calcd for $C_{33}H_{29}F_3N_2O_4$ + H+, 575.21522; found (ESI-FTMS, $[M+H]^{1+}$), 575.21382.

Example 10L: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-methoxybiphenyl-3-yl)ethyl]-L-α-glutamine

[0742] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-methoxybiphenyl-3-yl)ethyl]-L-α-glutaminate

HRMS: calcd for $C_{37}H_{40}N_2O_5$ + H+, 593.30100; found (ESI-FTMS, $[M+H]^{1+}$), 593.29993.

[0743] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-methoxybiphenyl-3-yl)ethyl]-L-α-glutamine

MS (ESI) *m/z* 537.2; HRMS: calcd for $C_{33}H_{32}N_2O_5$ + H+, 537.23840; found (ESI-FTMS, $[M+H]^{1+}$), 537.23745.

Example 10M: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-vinylbenzyl)-L-α-glutamine

[0744] Step A: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-vinylbenzyl)-L-α-glutaminate

Tert-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-iodobenzyl)-L-α-glutaminate was used as the starting material. MS (ESI) *m/z* 499.2; MS (ESI) *m/z* 997.4; HRMS: calcd for $C_{31}H_{34}N_2O_4$ + H+, 499.25913; found (ESI-FTMS, $[M+H]^{1+}$), 499.25906.

[0745] Step B: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-vinylbenzyl)-L-α-glutamine

MS (ESI) *m/z* 443.2; MS (ESI) *m/z* 885.3; HRMS: calcd for $C_{27}H_{26}N_2O_4$ + H+, 443.19653; found (ESI-FTMS, $[M+H]^{1+}$), 443.19728.

Example 10N: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-thien-2-ylbenzyl)-L-α-glutamine

[0746] Step A: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-thien-2-ylbenzyl)-L-α-glutaminate

Tert-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-iodobenzyl)-L-α-glutaminate was used as the starting material. MS (ESI) *m/z* 555.2; MS (ESI) *m/z* 1109.3; HRMS: calcd for $C_{33}H_{34}N_2O_4S$ + H+, 555.23120; found (ESI-FTMS, $[M+H]^{1+}$), 555.23173.

[0747] Step B: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-thien-2-ylbenzyl)-L-α-glutamine

MS (ESI) *m/z* 499.1; HRMS: calcd for $C_{29}H_{26}N_2O_4S$ + H+, 499.16860; found (ESI-FTMS, $[M+H]^{1+}$), 499.16976.

Example 10O: N^2-(biphenyl-4-ylcarbonyl)-N^1-{[4'-(trifluoromethyl)biphenyl-3-yl]methyl}-L-α-glutamine

[0748] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-{[4'-(trifluoromethyl)biphenyl-3-yl]methyl}-L-α-glutaminate

Tert-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-iodobenzyl)-L-α-glutaminate was used as the starting material. MS (ESI) *m/z* 617.2; MS (ESI) *m/z* 1233.3; HRMS: calcd for $C_{36}H_{35}F_3N_2O_4$ + H+, 617.26217; found (ESI-FTMS, $[M+H]^{1+}$), 617.26334.

[0749] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-{[4'-(trifluoromethyl)biphenyl-3-yl]methyl}-L-α-glutamine

MS (ESI) *m/z* 559.1; MS (ESI) *m/z* 1119.1; HRMS: calcd for $C_{32}H_{27}F_3N_2O_4$ + H+, 561.19957; found (ESI-FTMS, $[M+H]^{1+}$), 561.2001.

Example 10P: N^2-(biphenyl-4-ylcarbonyl)-N^1-[(4'-ethynylbiphenyl-3-yl)methyl]-L-α-glutamine

[0750] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-[(4'-ethynylbiphenyl-3-yl)methyl]-L-α-glutaminate

Tert-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-iodobenzyl)-L-α-glutaminate was used as the starting material. MS (ESI) *m/z* 573.2; MS (ESI) *m/z* 1145.4; HRMS: calcd for $C_{37}H_{36}N_2O_4$ + H+, 573.27478; found (ESI-FTMS, $[M+H]^{1+}$), 573.27518.

[0751] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-[(4'-ethynylbiphenyl-3-yl)methyl]-L-α-glutamine

MS (ESI) *m/z* 517.2; MS (ESI) *m/z* 1033.3; HRMS: calcd for $C_{33}H_{28}N_2O_4$ + H+, 517.21218; found (ESI-FTMS, $[M+H]^{1+}$), 517.2125.

Example 10Q: N^2-(biphenyl-4-ylcarbonyl)-N^1-(3-pyridin-2-ylbenzyl)-L-α-glutamine

[0752] Step A: *tert*-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(3-pyridin-2-ylbenzyl)-L-α-glutaminate

Tert-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-iodobenzyl)-L-α-glutaminate was used as the starting material. MS (ESI) *m/z* 550.2; HRMS: calcd for $C_{34}H_{35}N_3O_4$ + H+, 550.27003; found (ESI-FTMS, $[M+H]^{1+}$), 550.27066.

[0753] Step B: N^2-(biphenyl-4-ylcarbonyl)-N^1-(3-pyridin-2-ylbenzyl)-L-α-glutamine

MS (ESI) *m/z* 494.1; HRMS: calcd for $C_{30}H_{27}N_3O_4$ + H+, 494.20743; found (ESI-FTMS, $[M+H]^{1+}$), 494.20803.

Example 10R: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-vinylbenzyl)-L-α-glutamine

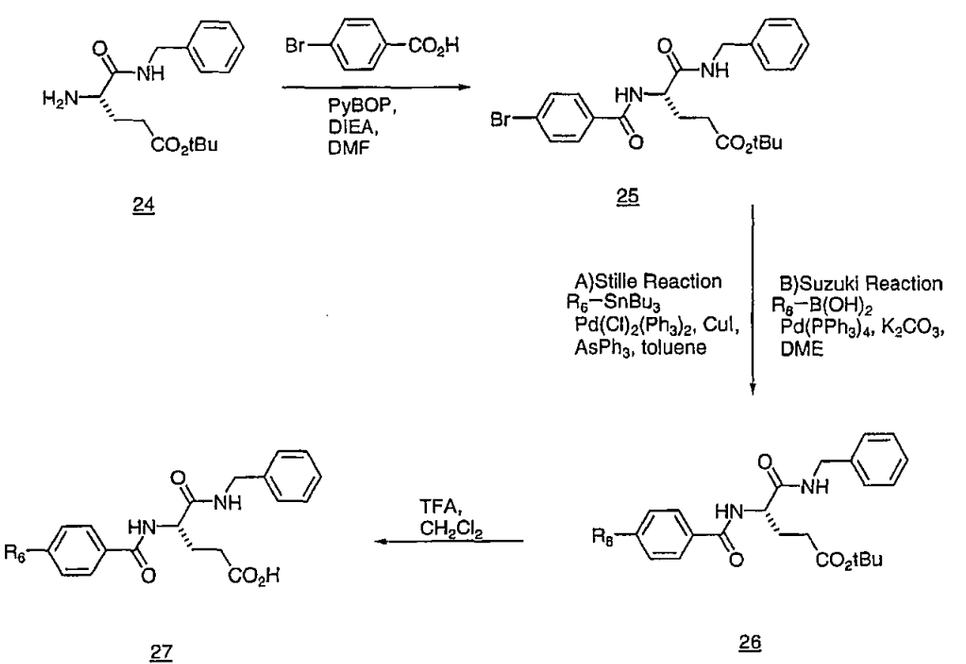
[0754] Step A: *tert*-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-vinylbenzyl)-L-α-glutaminate

Tert-butyl N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-iodobenzyl)-L-α-glutaminate was used as the starting material. MS (ESI) *m/z* 499.2; MS (ESI) *m/z* 997.3; HRMS: calcd for $C_{31}H_{34}N_2O_4$ + H+, 499.25913; found (ESI-FTMS, $[M+H]^{1+}$), 499.25883.

[0755] Step B: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-vinylbenzyl)-L-α-glutamine

MS (ESI) *m/z* 443.1; HRMS: calcd for $C_{27}H_{26}N_2O_4$ + H+, 443.19653; found (ESI-FTMS, $[M+H]^{1+}$), 443.19697.

Scheme 9



Example 11: N^1-benzyl-N^2-(4-thien-2-ylbenzoyl)-L-α-glutamine

[0756] Step A: *tert*-butyl N^1-benzyl-N^2-(4-bromobenzoyl)-L-α-glutaminate

A solution of 4-Amino-4-benzylcarbamoyl-butyric acid tert-butyl ester (6.39 g, 21.9

mmol, 1 equiv.) in DMF (18 mL) was added to 4-Bromobenzoic acid (4.39 g, 21.9 mmol, 1 equiv.) and PyBOP (14.7 g, 28.2 mmol, 1.2 equiv.) and the solution was stirred at room temperature under nitrogen. DIEA (4.58 mL, 26.3 mmol, 1.2 equiv.) was then added dropwise and the solution was stirred for 2 hrs. The reaction was complete as determined by TLC. The solution was diluted with EtOAc (250 mL) and washed consecutively with H_2O, 10% HCl, satd. $NaHCO_3$, brine, and dried over Na_2SO_4. After the solvent was evaporated, the crude residue was dissolved in ether and washed with aq. LiBr (2 x 250 mL) and dried over Na_2SO_4. A light tan solid was obtained, 8.94 g of *tert*-butyl N^1-benzyl-N^2-(4-bromobenzoyl)-L-α-glutaminate in 86 % yield.
MS (ESI) *m/z* 475.1; MS (ESI) *m/z* 949.2; HRMS: calcd for $C_{23}H_{27}BrN_2O_4$ + Na+, 497.10464; found (ESI_FTMS, $[M+Na]^{1+}$), 497.10542.

[0757] Step B: *tert*-butyl N^1-benzyl-N^2-(4-thien-2-ylbenzoyl)-L-α-glutaminate
Tert-butyl N^1-benzyl-N^2-(4-bromobenzoyl)-L-a-glutaminate (200mg, 0.421mmol) was dissolved in toluene (4mL) under nitrogen. Copper iodide (16.0mg, 0.0841mmol), triphenylarsine (26.0mg, 0.0841mmol), and $Pd(Cl)_2(PPh_3)_2$ (59mg, 0.0841mmol) were then added as solids. The reaction mixture was then fitted with a condenser and heated to reflux (115°C), for 10 minutes. 2-(Tributylstannyl)-thiophene (267mL, 0.841mmol) was added and immediately the reaction went from orange to black. These are typical Stille reaction conditions. The reaction was monitored by TLC and was complete at 30 minutes. The reaction mixture was filtered through celite and the celite rinsed with MeOH (1mL). Solvent was removed and the remaining yellow residue was dissolved in a minimal amount of CH_2Cl_2. Hexanes were added, precipitating a white solid that was filtered, washed with hexanes, and then dried at reduced pressure. 140mg of *tert*-butyl N^1-benzyl-N^2-(4-thien-2-ylbenzoyl)-L-α-glutaminate, a white solid was obtained in 69% yield. MS (ESI) *m/z* 479.1; MS (ESI) *m/z* 957.3; HRMS: calcd for $C_{27}H_{30}N_2O_4S$ + H+, 479.19990; found (ESI_FT, $[M+H]^{1+}$), 479.19826.

[0758] Step C: N^1-benzyl-N^2-(4-thien-2-ylbenzoyl)-L-α-glutamine
Tert-butyl N^1-benzyl-N^2-(4-thien-2-ylbenzoyl)-L-α-glutaminate (135mg, 0.282mmol) was dissolved in CH_2Cl_2 (1.5mL) under nitrogen. TFA was diluted in CH_2Cl_2 (2mL), and then added to the reaction. The reaction was monitored by TLC and was complete at 2 hrs. The solvent was removed and the remaining yellow residue was dissolved in toluene, which was then removed (2x) leaving an orange solid. The orange solid was taken up in

acetone, and hexanes added, precipitating a pale orange solid. The solid was filtered, washed with hexanes, and dried at reduced pressure. The pale orange solid was run on a SiO_2 column, using 4%MeOH/CH_2Cl_2. The solvent was removed from the fractions yielding 79mg of N^1-benzyl-N^2-(4-thien-2-ylbenzoyl)-L-α-glutamine, a white solid, at 66% yield. MS (ESI) *m/z* 421.1; MS (ESI) *m/z* 843.3; HRMS: calcd for $C_{23}H_{22}N_2O_4S$ + H+, 423.13730; found (ESI_FTMS, $[M+H]^{1+}$), 423.13742.

Example 12:

[0759] The following compounds were prepared according to procedures similar to those described in Example 11.

Example 12A: N^1-benzyl-N^2-[4-(2-furyl)benzoyl]-L-α-glutamine

[0760] Step B: *tert*-butyl N^1-benzyl-N^2-[4-(2-furyl)benzoyl]-L-α-glutaminate
MS (ESI) *m/z* 463.2; MS (ESI) *m/z* 925.3; HRMS: calcd for $C_{27}H_{30}N_2O_5$ + H+, 463.22275; found (ESI_FT, $[M+H]^{1+}$), 463.22159.

[0761] Step C: N^1-benzyl-N^2-[4-(2-furyl)benzoyl]-L-α-glutamine
MS (ESI) *m/z* 407.1; MS (ESI) *m/z* 813.2; HRMS: calcd for $C_{23}H_{22}N_2O_5$ + H+, 407.16015; found (ESI_FTMS, $[M+H]^{1+}$), 407.16031.

Example 12B: N^1-benzyl-N^2-[(4'-ethynyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0762] Step B: *tert*-butyl N^1-benzyl-N^2-[(4'-ethynyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate
MS (ESI) *m/z* 497.3; MS (ESI) *m/z* 993.5; HRMS: calcd for $C_{31}H_{32}N_2O_4$ + H+, 497.24348; found (ESI_FTMS, $[M+H]^{1+}$), 497.24306.

[0763] Step C: N^1-benzyl-N^2-[(4'-ethynyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine
MS (ESI) *m/z* 439.2; MS (ESI) *m/z* 879.4; HRMS: calcd for $C_{27}H_{24}N_2O_4$ + H+, 441.18088; found (ESI_FT, $[M+H]^{1+}$), 441.18056.

Example 12C: N^1-benzyl-N^2-(4-pyridin-3-ylbenzoyl)-L-α-glutamine

[0764] Step B: *tert*-butyl N^1-benzyl-N^2-(4-pyridin-3-ylbenzoyl)-L-α-glutaminate MS (ESI) *m/z* 474.2; HRMS: calcd for $C_{28}H_{31}N_3O_4$ + H+, 474.23873; found (ESI_FT, $[M+H]^{1+}$), 474.238741.

[0765] Step C: N^1-benzyl-N^2-(4-pyridin-3-ylbenzoyl)-L-α-glutamine MS (ESI) *m/z* 418.1; HRMS: calcd for $C_{24}H_{23}N_3O_4$ + H+, 418.17613; found (ESI_FT, $[M+H]^{1+}$), 418.17555.

Example 12D: N^1-benzyl-N^2-[4-(1,3-thiazol-2-yl)benzoyl]-L-α-glutamine

[0766] Step B: *tert*-butyl N^1-benzyl-N^2-[4-(1,3-thiazol-2-yl)benzoyl]-L-α-glutaminate

MS (ESI) *m/z* 480.2; MS (ESI) *m/z* 959.2; HRMS: calcd for $C_{26}H_{29}N_3O_4S$ + H+, 480.19515; found (ESI_FT, $[M+H]^{1+}$), 480.19659.

[0767] Step C: N^1-benzyl-N^2-[4-(1,3-thiazol-2-yl)benzoyl]-L-α-glutamine MS (ESI) *m/z* 422.2; MS (ESI) *m/z* 845.3; HRMS: calcd for $C_{22}H_{21}N_3O_4S$ + H+, 424.13255; found (ESI_FT, $[M+H]^{1+}$), 424.13204.

Example 12E: N^1-benzyl-N^2-(4-pyridin-2-ylbenzoyl)-L-α-glutamine

[0768] Step B: *tert*-butyl N^1-benzyl-N^2-(4-pyridin-2-ylbenzoyl)-L-α-glutaminate MS (ESI) *m/z* 474.2; HRMS: calcd for $C_{28}H_{31}N_3O_4$ + H+, 474.23873; found (ESI_FT, $[M+H]^{1+}$), 474.2401.

[0769] Step C: N^1-benzyl-N^2-(4-pyridin-2-ylbenzoyl)-L-α-glutamine MS (ESI) *m/z* 418.1; HRMS: calcd for $C_{24}H_{23}N_3O_4$ + H+, 418.17613; found (ESI_FT, $[M+H]^{1+}$), 418.17517.

Example 12F: N-benzyl-N^2-[4-(2-naphthyl)benzoyl]-L-α-glutamine

[0770] MS (ESI) m/z 467.2; MS (ESI) m/z 933.4; HRMS: calcd for $C_{29}H_{26}N_2O_4$ + H+, 467.19653; found (ESI-FTMS, $[M+H]^{1+}$), 467.19661.

Example 12G: N-benzyl-N^2-[4-(phenylethynyl)benzoyl]-L-α-glutamine

[0771] MS (ESI) m/z 441.2; MS (ESI) m/z 881.4.

Example 12H: N-benzyl-N^2-{4-[(9-hydroxy-9H-fluoren-9-yl)ethynyl]benzoyl}-L-α-glutamine

[0772] MS (ESI) m/z 543.1; MS (ESI) m/z 1087.2.

Example 12I: N-benzyl-N^2-{4-[(1E)-3-oxo-3-phenylprop-1-en-1-yl]benzoyl}-L-α-glutamine

[0773] MS (ESI) m/z 471.2; MS (ESI) m/z 941.4.

Example 12J: N^2-{4-[(3-aminophenyl)ethynyl]benzoyl}-N-benzyl-L-α-glutamine

[0774] MS (ESI) m/z 456.1; MS (ESI) m/z 249.1.

Example 12K: N-benzyl-N^2-[4-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)benzoyl]-L-α-glutamine

[0775] MS (ESI) m/z 545.1; MS (ESI) m/z 1091.2; MS (ESI) m/z 659.1.

Example 12L: N-benzyl-N^2-{4-[(3-methoxyphenyl)ethynyl]benzoyl}-L-α-glutamine

[0776] MS (ESI) m/z 471.1; MS (ESI) m/z 941.2.

Example 13:

[0777] The following compounds were prepared according to procedures similar to those described in Example 11, except a Suzuki reaction was used at step B in place of a Stille reaction. Hydrolysis of the ester to the final product followed the same procedure as previously described.

Example 13A: *N*^{1}-benzyl-*N*^{2}-[(3',5'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0778] Step B: *tert*-butyl *N*^{1}-benzyl-*N*^{2}-[(3',5'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate

Tert-butyl N^1-benzyl-N^2-(4-bromobenzoyl)-L-α-glutaminate (350mg, 0.736mmol) was dissolved in DME, under nitrogen in a sealed vial. 3,5-Dimethylboronic acid (110mg, 0.736mmol), and $Pd(PPh_3)_4$ (43mg, 0.037mmol) were added as solids, and the reaction heated to reflux for 10 minutes. At this point 2M K_2CO_3 (735mL, 1.47mmol) was added,

the reaction vial was sealed, and the reaction heated to reflux and monitored by TLC. The reaction was complete at 2 hrs. The aqueous part of the reaction was removed via pipette. The reaction solution was then filtered through celite and the celite rinsed with MeOH. The solvent was removed, leaving a brown solid. The product was purified using a SiO_2 column and 33%EtOAc/Hex as the solvent. The product was obtained as a white solid, yielding 222mg at 60% yield. MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.6; HRMS: calcd for $C_{31}H_{36}N_2O_4$ + H+, 501.27478; found (ESI_FT, $[M+H]^{1+}$), 501.27332.

[0779] Step C: N^1-benzyl-N^2-[(3',5'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

MS (ESI_FT) *m/z* 445.21151; MS (ESI_FT) *m/z* 445.21219; HRMS: calcd for $C_{27}H_{28}N_2O_4$ + H+, 445.21218; found (ESI_FT, $[M+H]^{1+}$), 445.21151.

Example 13B: N^1-benzyl-N^2-[(2',5'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0780] Step B: *tert*-butyl N^1-benzyl-N^2-[(2',5'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.6; HRMS: calcd for $C_{31}H_{36}N_2O_4$ + H+, 501.27478; found (ESI_FT, $[M+H]^{1+}$), 501.27441.

[0781] Step C: N^1-benzyl-N^2-[(2',5'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

MS (ESI) *m/z* 445.3; MS (ESI) *m/z* 889.5; HRMS: calcd for $C_{27}H_{28}N_2O_4$ + H+, 445.21218; found (ESI_FT, $[M+H]^{1+}$), 445.21172.

Example 13C: N^1-benzyl-N^2-[(4'-ethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0782] Step B: *tert*-butyl N^1-benzyl-N^2-[(4'-ethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.6; HRMS: calcd for $C_{31}H_{36}N_2O_4$ + H+, 501.27478; found (ESI_FT, $[M+H]^{1+}$), 501.27326.

[0783] Step C: N^1-benzyl-N^2-[(4'-ethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

MS (ESI_FT) *m/z* 445.2115; MS (ESI_FT) *m/z* 445.21219; HRMS: calcd for $C_{27}H_{28}N_2O_4$ + H+, 445.21218; found (ESI_FT, $[M+H]^{1+}$), 445.2115.

Example 13D: N^1-benzyl-N^2-[(3'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0784] Step B: *tert*-butyl N^1-benzyl-N^2-[(3'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1033.6; HRMS: calcd for $C_{31}H_{36}N_2O_5$ + H+, 517.26970; found (ESI_FT, $[M+H]^{1+}$), 517.26837.

[0785] Step C: N^1-benzyl-N^2-[(3'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

MS (ESI_FT) *m/z* 461.20568; MS (ESI_FT) *m/z* 461.2071; HRMS: calcd for $C_{27}H_{28}N_2O_5$ + H+, 461.20710; found (ESI_FT, $[M+H]^{1+}$), 461.20568.

Example 13E: N^1-benzyl-N^2-[(2'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0786] Step B: *tert*-butyl N^1-benzyl-N^2-[(2'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1033.5; HRMS: calcd for $C_{31}H_{36}N_2O_5$ + H+, 517.26970; found (ESI_FT, $[M+H]^{1+}$), 517.26833.

[0787] Step C: N^1-benzyl-N^2-[(2'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

MS (ESI_FT) *m/z* 461.20572; MS (ESI_FT) *m/z* 461.2071; HRMS: calcd for $C_{27}H_{28}N_2O_5$ + H+, 461.20710; found (ESI_FT, $[M+H]^{1+}$), 461.20572.

Example 13F: N^1-benzyl-N^2-[(2',6'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0788] Step B: *tert*-butyl N^1-benzyl-N^2-[(2',6'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate

MS (ESI_FT) *m/z* 501.27323; MS (ESI_FT) *m/z* 501.27479; HRMS: calcd for $C_{31}H_{36}N_2O_4$ + H+, 501.27478; found (ESI_FT, $[M+H]^{1+}$), 501.27323.

[0789] Step C: N^1-benzyl-N^2-[(2',6'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

MS (ESI_FT) *m/z* 445.21145; MS (ESI_FT) *m/z* 445.21219; HRMS: calcd for $C_{27}H_{28}N_2O_4$ + H+, 445.21218; found (ESI_FT, $[M+H]^{1+}$), 445.21145.

Example 13G: N^1-benzyl-N^2-[(4'-vinyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

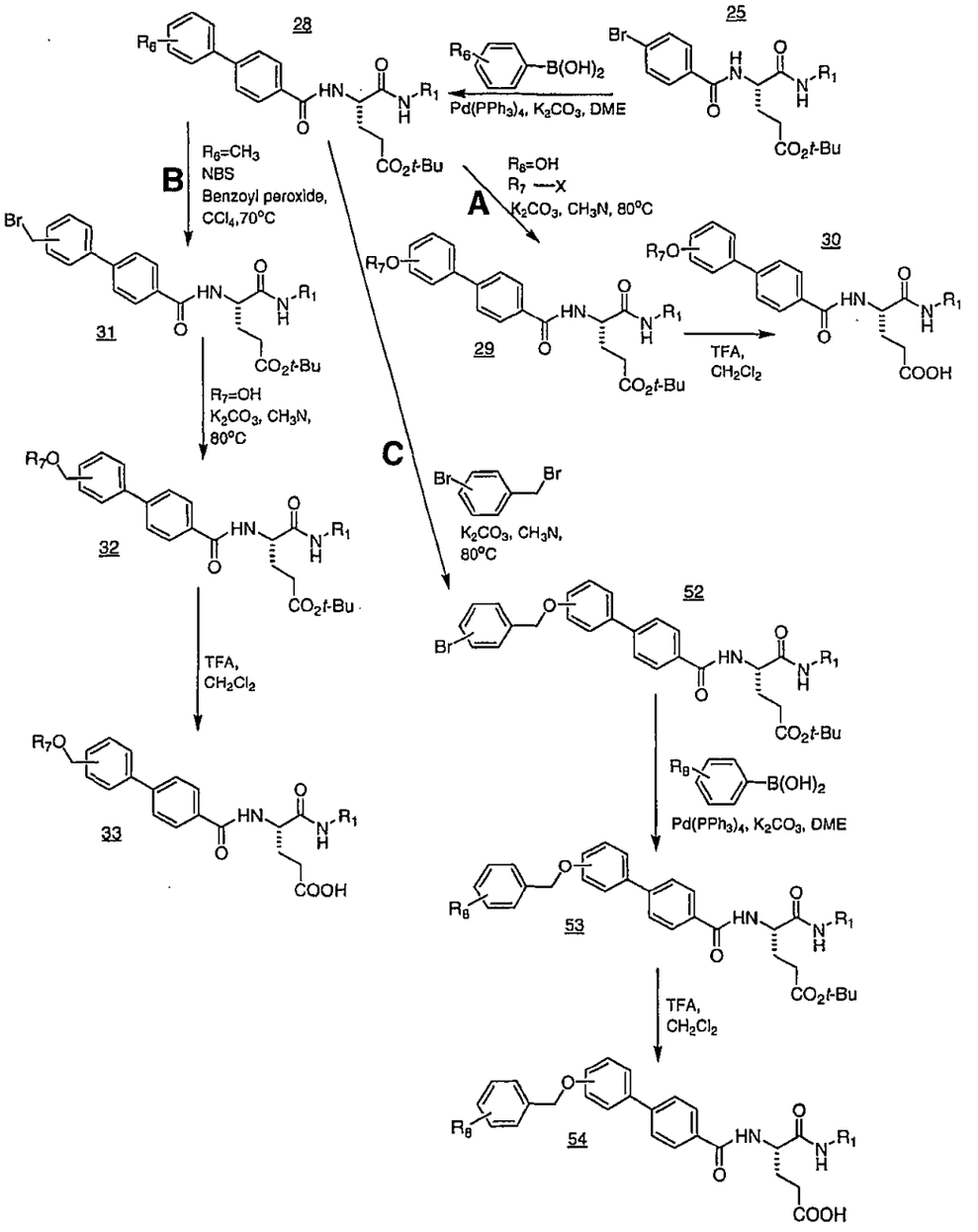
[0790] Step B: *tert*-butyl N^1-benzyl-N^2-[(4'-vinyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 499.3; MS (ESI) *m/z* 997.5; HRMS: calcd for $C_{31}H_{34}N_2O_4$ + H+, 499.25913; found (ESI_FT, $[M+H]^{1+}$), 499.25855.

[0791] Step C: N^1-benzyl-N^2-[(4'-vinyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

MS (ESI) *m/z* 443.2; MS (ESI) *m/z* 885.4; HRMS: calcd for $C_{27}H_{26}N_2O_4$ + H+, 443.19653; found (ESI-FTMS, $[M+H]^{1+}$), 443.19675.

Scheme 10



Example 14: N^1-benzyl-N^2-[(4'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0792] Step A: *tert*-butyl N^1-benzyl-N^2-[(4'-hydroxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate

Tert-butyl N^1-benzyl-N^2-(4-bromobenzoyl)-L-α-glutaminate (3.00g,6.31mmol) was dissolved in DME (40mL), under nitrogen in a 75mL bomb flask. 4-Hydroxyphenylboronic acid (871mg, 6.31mmol), and $Pd(PPh_3)_4$ (729mg, 0.631mmol)

were added as solids, and the reaction heated to reflux for 30 minutes. At this point K_2CO_3 (1.74g, 12.6mmol) was dissolved in H_2O (8mL), and added to the reaction. The bomb flask was sealed and the reaction was heated to reflux, stirred overnight, and monitored by TLC. The reaction was complete after stirring overnight. The reaction mixture was filtered through celite and the celite rinsed with MeOH. The solvent was removed and the remaining solid was dissolved in EtOAc (200mL) and then washed with 200mL of 10% HCl (2x) and brine. The organic layer (top) was then dried (Na_2SO_4), filtered and concentrated, leaving a dark red oily solid. The product was purified using a SiO_2 column, and 40%Ace/Hex as the solvent. It would not dissolve in this solvent so it was dissolved in Acetone/MeOH (1:1) and dry mounted on the column. The product was obtained as the third spot of the column and as a yellow solid. Yield 1.9g of *tert*-butyl N^1-benzyl-N^2-[(4'-hydroxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate at 62% yield. MS (ESI) *m/z* 487.4; MS (ESI) *m/z* 533.5; MS (ESI) *m/z* 975.8; HRMS: calcd for $C_{29}H_{32}N_2O_5$ + H+, 489.23840; found (ESI_FTMS, $[M+H]^{1+}$), 489.23862.

[0793] Step B: *tert*-butyl N^1-benzyl-N^2-[(4'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate

Tert-butyl N^1-benzyl-N^2-[(4'-hydroxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate (300mg, 0.614mmol) was dissolved in CH_3CN (7mL) in a sealed 20mL vial. K_2CO_3 was added as a solid, the vial sealed and heated to 80°C for 1 hour. Iodoethane (54mL, 0.675mmol) was added, the vial sealed and stirred at 80°C overnight. The reaction was monitored by TLC and was complete after stirring overnight. The solvent was removed via nitrogen blower, and the remaining solid dissolved in CH_2Cl_2 (7mL) and washed with 10% HCl (7mL). The aqueous layer was decanted with a pipette, and the solvent was removed via nitrogen blower. The remaining solid was dissolved in DMSO (2mL) and purified on a Gilson HPLC. Yield: 123mg of *tert*-butyl N^1-benzyl-N^2-[(4'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate, a white solid at 39% yield. MS (ESI) *m/z* 517.2; MS (ESI) *m/z* 1033.4; HRMS: calcd for $C_{31}H_{36}N_2O_5$ + H+, 517.26970; found (ESI_FTMS, $[M+H]^{1+}$), 517.26801.

[0794] Step C: N^1-benzyl-N^2-[(4'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

The procedure used was similar to that described in Example 13. MS (ESI) *m/z* 461.2; MS (ESI) *m/z* 921.4; HRMS: calcd for $C_{27}H_{28}N_2O_5$ + H+, 461.20710; found (ESI_FTMS, $[M+H]^{1+}$), 461.20542.

Example 15:

[0795] The following compounds were prepared according to procedures similar to those described in Example 14.

Example 15A: N^1-benzyl-N^2-[(4'-propoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0796] Step B: *tert*-butyl N^1-benzyl-N^2-[(4'-propoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 531.3; MS (ESI) *m/z* 1061.4; HRMS: calcd for $C_{32}H_{38}N_2O_5$ + H+, 531.28535; found (ESI_FTMS, $[M+H]^{1+}$), 531.2844.

[0797] Step C: N^1-benzyl-N^2-[(4'-propoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

MS (ESI) *m/z* 475.2; MS (ESI) *m/z* 949.4; HRMS: calcd for $C_{28}H_{30}N_2O_5$ + H+, 475.22275; found (ESI_FTMS, $[M+H]^{1+}$), 475.22333.

Example 15B: N^1-benzyl-N^2-[(4'-butoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0798] Step B: *tert*-butyl N^1-benzyl-N^2-[(4'-butoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 545.3; MS (ESI) *m/z* 1089.5; HRMS: calcd for $C_{33}H_{40}N_2O_5$ + H+, 545.30100; found (ESI_FTMS, $[M+H]^{1+}$), 545.30048.

[0799] Step C: N^1-benzyl-N^2-[(4'-butoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

MS (ESI) *m/z* 489.3; MS (ESI) *m/z* 977.4; HRMS: calcd for $C_{29}H_{32}N_2O_5$ + H+, 489.23840; found (ESI_FTMS, $[M+H]^{1+}$), 489.23871.

Example 15C: N^1-benzyl-N^2-{[4'-(cyclobutylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine

[0800] Step B: *tert*-butyl N^1-benzyl-N^2-{[4'-(cyclobutylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutaminate

MS (ESI) *m/z* 557.3; MS (ESI) *m/z* 1113.4; HRMS: calcd for $C_{34}H_{40}N_2O_5$ + H+, 557.30100; found (ESI_FTMS, $[M+H]^{1+}$), 557.30064.

[0801] Step C: N^1-benzyl-N^2-{[4'-(cyclobutylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine

MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.5; HRMS: calcd for $C_{30}H_{32}N_2O_5$ + H+, 501.23840; found (ESI_FTMS, $[M+H]^{1+}$), 501.23937.

Example 15D: N^1-benzyl-N^2-{[4'-(cyclohexylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine

[0802] Step B: *tert*-butyl N^1-benzyl-N^2-{[4'-(cyclohexylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutaminate

MS (ESI) *m/z* 585.3; MS (ESI) *m/z* 1169.5; HRMS: calcd for $C_{36}H_{44}N_2O_5$ + H+, 585.33230; found (ESI_FTMS, $[M+H]^{1+}$), 585.33275.

[0803] Step C: N^1-benzyl-N^2-{[4'-(cyclohexylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine

MS (ESI) *m/z* 529.3; MS (ESI) *m/z* 1057.5; HRMS: calcd for $C_{32}H_{36}N_2O_5$ + H+, 529.26970; found (ESI_FTMS, $[M+H]^{1+}$), 529.27022.

Example 15E: N^2-{[4'-(allyloxy)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutamine

[0804] Step B: *tert*-butyl N^2-{[4'-(allyloxy)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutaminate

MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.4; HRMS: calcd for $C_{32}H_{36}N_2O_5$ + H+, 529.26970; found (ESI_FTMS, $[M+H]^{1+}$), 529.26804.

[0805] Step C: N^2-{[4'-(allyloxy)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutamine

Example 15F: N^1-benzyl-N^2-({4'-[(3-methoxybenzyl)oxy]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutamine

[0806] Step B: *tert*-butyl N^1-benzyl-N^2-({4'-[(3-methoxybenzyl)oxy]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutaminate

MS (ESI) *m/z* 609.3; MS (ESI) *m/z* 1217.5; HRMS: calcd for $C_{37}H_{40}N_2O_6$ + H+, 609.29591; found (ESI-FTMS, $[M+H]^{1+}$), 609.29669.

[0807] Step C: N^1-benzyl-N^2-({4'-[(3-methoxybenzyl)oxy]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutamine

MS (ESI) *m/z* 553.2; MS (ESI) *m/z* 1105.3; HRMS: calcd for $C_{33}H_{32}N_2O_6$ + H+, 553.23331; found (ESI-FTMS, $[M+H]^{1+}$), 553.23235.

Example 15G: N^1-benzyl-N^2-({4'-[(3,5-dimethoxybenzyl)oxy]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutamine

[0808] Step B: *tert*-butyl N^1-benzyl-N^2-({4'-[(3,5-dimethoxybenzyl)oxy]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutaminate

MS (ESI) *m/z* 639.3; MS (ESI) *m/z* 1277.4; HRMS: calcd for $C_{38}H_{42}N_2O_7$ + H+, 639.30648; found (ESI-FTMS, $[M+H]^{1+}$), 639.30698.

[0809] Step C: N^1-benzyl-N^2-({4'-[(3,5-dimethoxybenzyl)oxy]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutamine

MS (ESI) *m/z* 583.2; MS (ESI) *m/z* 1165.3; HRMS: calcd for $C_{34}H_{34}N_2O_7$ + H+, 583.24388; found (ESI-FTMS, $[M+H]^{1+}$), 583.2433.

Example 15H: N^1-benzyl-N^2-{[4'-(2-naphthylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine

[0810] Step B: *tert*-butyl N^1-benzyl-N^2-{[4'-(2-naphthylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutaminate

MS (ESI) *m/z* 629.3; HRMS: calcd for $C_{40}H_{40}N_2O_5$ + H+, 629.30100; found (ESI-FTMS, $[M+H]^{1+}$), 629.30277.

[0811] Step C: N^1-benzyl-N^2-{[4'-(2-naphthylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine

MS (ESI) *m/z* 571.3; HRMS: calcd for $C_{36}H_{32}N_2O_5$ + H+, 573.23840; found (ESI-FTMS, $[M+H]^{1+}$), 573.23779.

Example 15I: N-benzyl-N^2-({4'-[(3-fluorobenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutamine

[0812] MS (ESI) m/z 541.1; MS (ESI) m/z 1081.2.

Example 15J: N-benzyl-N^2-{[4'-(benzyloxy)biphenyl-4-yl]carbonyl}-L-α-glutamine

[0813] MS (ESI) m/z 523.1; MS (ESI) m/z 1045.2.

[0814] The following compounds were prepared according to Scheme 10, Route A:

Example 15K: *N*^{2}-{[3'-(benzyloxy)biphenyl-4-yl]carbonyl}-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0815] MS (ESI) *m/z* 613.1; MS (ESI) *m/z* 1225.1; HRMS: calcd for $C_{35}H_{36}N_2O_8$ + H+, 613.25444; found (ESI-FTMS, $[M+H]^{1+}$), 613.25451.

Example 15L: *N*^{2}-({3'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0816] MS (ESI) *m/z* 673.3; MS (ESI) *m/z* 1345.6; MS (ESI) *m/z* 690.4; HRMS: calcd for $C_{37}H_{40}N_2O_{10}$ + H+, 673.27557; found (ESI-FTMS, $[M+H]^{1+}$), 673.27431.

Example 15M: *N*^{2}-({3'-[(3-methoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0817] MS (ESI) *m/z* 643.3; MS (ESI) *m/z* 1285.6; HRMS: calcd for $C_{36}H_{38}N_2O_9$ + H+, 643.26501; found (ESI-FTMS, $[M+H]^{1+}$), 643.26574.

Example 15N: *N*^{2}-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0818] MS (ESI) *m/z* 643.3; MS (ESI) *m/z* 1285.6; HRMS: calcd for $C_{37}H_{39}FN_2O_7$ + H+, 643.28141; found (ESI-FTMS, $[M+H]^{1+}$), 643.28187.

[0819] The following compounds were prepared according to Scheme 10, Route B:

Example 15O: N^2-[(4'-{[3,5-bis(trifluoromethyl)phenoxy]methyl}biphenyl-4-yl)carbonyl]- *N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0820] Step A: *tert*-butyl *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-methylbiphenyl-4-yl)carbonyl]-L-α-glutaminate

tert-butyl N^1-benzyl-N^2-(4-bromobenzoyl)-L-α-glutaminate (1.00g, 1.93mmol) was dissolved in DME (10mL) under nitrogen and placed in a microwave vial. 4-methylphenyl boronic acid (526mg, 3.87.mmol), and $Pd(PPh_3)_4$ (334mg, 0.290mmol) were added as solids prior to the addition of K_2CO_3 (800mg, 5.79mmol) dissolved in H_2O (2.3mL). The vial was sealed and heated to 80°C in a microwave for 20 minutes. The solvent was removed and the remaining yellow oil was dissolved in diethyl ether (125mL). The organics were washed consecutively with 10% HCl (125mL), water (125mL) and brine (125mL). The organic layer was dried with $MgSO_4$, filtered through celite and the solvent was removed. The sticky solid was purified using on a 40g Combi flash column using an increasing gradient of EtOAc/Hex as the solvent. The product was obtained as a light brown solid. Yield 792 mg of *tert*-butyl *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-methylbiphenyl-4-yl)carbonyl]-L-α-glutaminate at 78% yield. MS (ESI) *m/z* 529.3; HRMS: calcd for $C_{33}H_{40}N_2O_4$ + H+, 529.30608; found (ESI-FTMS, $[M+H]^{1+}$), 529.30594.

[0821] Step B: *tert*-butyl N^2-{[4'-(bromomethyl)biphenyl-4-yl]carbonyl}-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutaminate

tert-butyl *N*-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-methylbiphenyl-4-yl)carbonyl]-L-α-glutaminate (3.5g, 6.62mmol) was dissolved in CCl_4 (50mL) along with *N*-Bromosuccinimide (2.36g, 13.2mmol) and benzoyl peroxide (321mg, 1.32mmol) in a 100mL flask equipped with a reflux condenser. The reaction mixture stirred overnight at 70°C. The solvent was removed and the residue was purified using a SiO2 column and 20%EtOAc/Hex as the solvent giving a yellow solid. Yield 1.05g *tert*-butyl N^2-{[4'-(bromomethyl)biphenyl-4-yl]carbonyl}-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutaminate at 57% yield. MS (ESI) *m/z* 607.1; HRMS: calcd for $C_{33}H_{39}BrN_2O_4$ + H+, 607.21660; found (ESI-FTMS, $[M+H]^{1+}$), 607.21591.

[0822] Step C: *tert*-butyl N^2-[(4'-{[3,5-bis(trifluoromethyl)phenoxy]methyl}biphenyl-4- yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutaminate

tert-butyl N^2-{[4'-(bromomethyl)biphenyl-4-yl]carbonyl}-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutaminate (253mg,0.41mmol) 3,5-bis(trifluoromethyl)phenol (63μL,.42mmol) and K_2CO_3 (287mg, 2.08mmol) were all combined in a 10mL vial. Acetonitrile (4mL) was added dissolving some of the solids upon heating to 80°C. The reaction was monitored using TLC and MS. The reaction was stirred overnight (18h). The reaction was filtered using a fritted funnel and the solvent was removed. The filtrate was collected and the solvent was removed. The residue was purified using a SiO_2 column and 20%EtOAc/Hex as the solvent giving a white solid. Yield 242mg of *tert*-butyl N^2-[(4'-{[3,5-bis(trifluoromethyl)phenoxy]methyl}biphenyl-4- yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutaminate at 77% yield. MS (ESI) *m/z* 757.4; HRMS: calcd for $C_{41}H_{42}F_6N_2O_5$ + H+, 757.30707; found (ESI-FTMS, $[M+H]^{1+}$), 757.30532.

[0823] Step D: N^2-[(4'-{[3,5-bis(trifluoromethyl)phenoxy]methyl}biphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

tert-butyl N^2-[(4'-{[3,5-bis(trifluoromethyl)phenoxy]methyl}biphenyl-4- yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutaminate (215mg,0.284mmol) was dissolved in CH_2Cl_2 (3mL) and stirred in a 10mL flask. Trifluoroacetic acid (1.09mL, 14mmol) was added and the solution was stirred for 2 hours. The solvent was removed and the dried under vacuum. The resulting residue was purified using preparative HPLC (ACN/H_2O, 0.02% TFA). The main peak fractions were collected and after removal of solvent gave the product as a white solid. Yield of 104 mg of N^2-[(4'-{[3,5-bis(trifluoromethyl) phenoxy]methyl} biphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine was obtained in 52% yield. MS (ESI) *m/z* 699.3; HRMS: calcd for $C_{37}H_{34}F_6N_2O_5$ + H+, 701.24447; found (ESI-FTMS, $[M+H]^{1+}$), 701.24429.

[0824] The following compounds were prepared according to the procedure described above for example 15O:

Example 15P: N^2-({4'-[(1,3-benzodioxol-5-yloxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0825] MS (ESI) *m/z* 609.3; MS (ESI) *m/z* 1217.6; HRMS: calcd for $C_{36}H_{36}N_2O_7$ + H+, 609.25953; found (ESI-FTMS, $[M+H]^{1+}$), 609.26109.

Example 15Q: N^2-({4'-[(3,5-dimethoxyphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(3-methylbenzyl)-L-α-glutamine

[0826] MS (ESI) *m/z* 595.4; HRMS: calcd for $C_{35}H_{36}N_2O_7$ + H+, 597.25953; found (ESI-FTMS, $[M+H]^{1+}$), 597.25901.

Example 15R: N^2-({3'-[(3,5-dimethoxyphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(3-methylbenzyl)-L-α-glutamine

[0827] MS (ESI) *m/z* 595.2; HRMS: calcd for $C_{35}H_{36}N_2O_7$ + H+, 597.25953; found (ESI-FTMS, $[M+H]^{1+}$), 597.2593.

Example 15S: N^2-[(3'-{[3,5-bis(trifluoromethyl)phenoxy]methyl}biphenyl-4-yl)carbonyl]-*N*-(3-methylbenzyl)-L-α-glutamine

[0828] MS (ESI) *m/z* 671.2; MS (ESI) *m/z* 1343.7; HRMS: calcd for $C_{35}H_{30}F_6N_2O_5$ + H+, 673.21317; found (ESI-FTMS, $[M+H]^{1+}$), 673.21279.

Example 15T: N^2-({3'-[(3-ethylphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(3-methylbenzyl)-L-α-glutamine

[0829] MS (ESI) *m/z* 563.3; HRMS: calcd for $C_{35}H_{36}N_2O_5$ + H+, 565.26970; found (ESI-FTMS, $[M+H]^{1+}$), 565.26999.

[0830] The following compounds were prepared according to Scheme 10, Route C:

Example 15U: *N*-benzyl-N^2-{[4'-(biphenyl-3-ylmethoxy)biphenyl-4-yl]carbonyl}-L-α-glutamine

[0831] Step A: *tert*-butyl N^1-benzyl-N^2-[(4'-hydroxy-1,1'-biphenyl-4-yl)carbonyl]-L-α- glutaminate

tert-butyl N^1-benzyl-N^2-(4-bromobenzoyl)-L-α-glutaminate (2.00g,4.21mmol) was dissolved in DME (20mL) under nitrogen and placed in a 75mL flask. 4-Hydroxyphenyl

boronic acid (638mg, 4.63.mmol), and $Pd(PPh_3)_4$ (729mg, 0.632mmol) were added as solids prior to the addition of K_2CO_3 (1.75g,12.6mmol) dissolved in H_2O (5mL). The flask was sealed and the reaction was heated to reflux, stirred for two days and monitored by TLC. The reaction mixture was filtered through celite and thne rinsed with MeOH. The solvent was removed and the resulting residue was purified using a SiO2 column and 33%EtOAc/Hex as the solvent. The product was obtained as a white solid. Yield: 514 mg of *tert*-butyl N^1-benzyl-N^2-[(4'-hydroxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutaminate at 25% yield. MS (ESI) *m/z* 487.4; HRMS: calcd for $C_{29}H_{32}N_2O_5$ + H+, 489.23840; found (ESI_FTMS, $[M+H]^{1+}$), 489.23862.

[0832] Step B: *tert*-butyl *N*-benzyl-N^2-({4'-[(3-bromobenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutaminate

3,3-bromobenzylbromide and K_2CO_3 were all combined in a 20mL vial. CH_3CN (6mL) was added, dissolving some of the solids upon heating to 80°C. The reaction was monitored using TLC and MS. After 2 hours the reaction was complete. The resulting product quickly precipitated upon cooling of the CH_3CN. The reaction was filtered using a fritted funnel and the filtrate was collected and redissolved in warm CH_3CN. The solution was allowed to crystallize overnight in the freezer. The white solid was collected and washed with cold CH_3CN. Yield: 357mg of *tert*-butyl *N*-benzyl-N^2-({4'-[(3-bromobenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutaminate at 57% yield. MS (ESI) *m/z* 657.2.

[0833] Step C: *tert*-butyl *N*-benzyl-N^2-{[4'-(biphenyl-3-ylmethoxy)biphenyl-4-yl]carbonyl}-L-α-glutaminate

tert-butyl *N*-benzyl-N^2-({4'-[(3-bromobenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutaminate (250mg, 0.38mmol) was dissolved in DME (5mL) under nitrogen in a 75mL bomb flask. Phenylboronic acid (51mg, 0.418mmol), and $Pd(PPh_3)_4$ (66mg,0.057mmol) were added as solids prior to the addition of K_2CO_3 (158mg,1.14mmol) dissolved in H_2O (1.5mL). The bomb flask was sealed and the reacton was heated to reflux, stirred two days and monitored by TLC. The reaction mixture was filtered through celite and the celite rinsed with MeOH. The solvent was removed and the resulting residue was purified using preparative HPLC. The product was obtained as a pale orange solid. Yield: 154 mg of *tert*-butyl *N*-benzyl-N^2-{[4'-(biphenyl-3-ylmethoxy)biphenyl-4-

yl]carbonyl}-L-α-glutaminate at 60% yield. MS (ESI) *m/z* 655.5; HRMS: calcd for $C_{42}H_{42}N_2O_5$ + H+, 655.31665; found (ESI-FTMS, $[M+H]^{1+}$), 655.31636.

[0834] Step D: *N*-benzyl-N^2-{[4'-(biphenyl-3-ylmethoxy)biphenyl-4-yl]carbonyl}-L-α- glutamine

tert-butyl *N*-benzyl-N^2-{[4'-(biphenyl-3-ylmethoxy)biphenyl-4-yl]carbonyl}-L-α-glutaminate (130mg,0.199mmol) was dissolved in CH_2Cl_2 (3mL) and stirred in a 10mL flask. Trifluoroacetic acid (765uL, 10mmol) was added and the solution was stirred for 2 hours. The solvent was removed and the dried under vacuum. The orange residue was dissolved in minimum acetone and precipitated with hexanes. Yield of 109 mg of *N*-benzyl-N^2-{[4'-(biphenyl-3-ylmethoxy)biphenyl-4-yl]carbonyl}-L-α- glutamine was obtained in 91% yield. MS (ESI) *m/z* 599.4; HRMS: calcd for $C_{38}H_{34}N_2O_5$ + H+, 599.25405; found (ESI-FTMS, $[M+H]^{1+}$), 599.25511.

Example 15V: *N*-benzyl-N^2-({4'-[(3'-methoxybiphenyl-3-yl)methoxy]biphenyl-4-yl}carbonyl)-L-α-glutamine

[0835] MS (ESI) *m/z* 627.2; HRMS: calcd for $C_{39}H_{36}N_2O_6$ + H+, 629.26461; found (ESI-FTMS, $[M+H]^{1+}$), 629.26493.

Example 15W: *N*-benzyl-N^2-{[4'-(biphenyl-2-ylmethoxy)biphenyl-4-yl]carbonyl}-L-α-glutamine

[0836] MS (ESI) *m/z* 597.3; HRMS: calcd for $C_{38}H_{34}N_2O_5$ + H+, 599.25405; found (ESI-FTMS, $[M+H]^{1+}$), 599.25523.

Example 15X: *N*-benzyl-N^2-({4'-[(3'-methoxybiphenyl-2-yl)methoxy]biphenyl-4-yl}carbonyl)-L-α-glutamine

[0837] MS (ESI) *m/z* 627.3; HRMS: calcd for $C_{39}H_{36}N_2O_6$ + H+, 629.26461; found (ESI-FTMS, $[M+H]^{1+}$), 629.26484.

Example 15Y: N^2-({4'-[(3-tert-butylphenoxy)methyl]biphenyl-4-yl}carbonyl)-N-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0838] Tolyl-biphenylglutamate (1g, 1.89mmol) was dissolved in CCl_4 (20mL), in a 40mL sealed vial. N-Bromosuccinimide (NBS) (673mg, 3.78mmol) and Benzoyl

peroxide (92mg, 0.378mmol) were added. The reaction was heated to 70°C, and stirred overnight. The reaction was cooled and the solvent removed. The remaining sticky orange solid was purified by silica column chromatography using 20%EtOAc/ Hexanes. 400mg of Bromo-tolyl-biphenylglutamate was obtained, as a pale yellow solid at 36% yield.

[0839] 3-*t*-Butylphenol (56mg, 0.374mmol) was dissolved in CH_3CN in a 20ml sealed vial and K_2CO_3 (258mg, 1.87mmol) was added. The reaction was heated to 80°C and stirred for 30 minutes. The Bromo-tolyl-biphenylglutamate (250mg, 0.411mmol) was added and the reaction stirred at 80°C overnight. The reaction was filtered, the solvent was removed and the remainder of the reaction was purified by silica column chromatography to give the title compound as a white solid was obtained in 87% yield.

[0840] MS (ESI) m/z 621.2; MS (ESI) m/z 1241.4; HRMS: calcd for $C_{39}H_{44}N_2O_5$ + H+, 621.33230; found (ESI-FTMS, $[M+H]^{1+}$), 621.33234.

[0841] The following compounds were prepared according to procedures similar to those described in Example 15Y:

Example 15Z: N^2-({4'-[(3,5-di-tert-butylphenoxy)methyl]biphenyl-4-yl}carbonyl)-N-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0842] MS (ESI) m/z 675.3; MS (ESI) m/z 1351.6; HRMS: calcd for $C_{43}H_{52}N_2O_5$ + H+, 677.39490; found (ESI-FTMS, $[M+H]^{1+}$), 677.39504.

Example 15AA: N-(1,1-dimethyl-2-phenylethyl)-N^2-({4'-[(3-ethylphenoxy)methyl]biphenyl-4-yl}carbonyl)-L-α-glutamine

[0843] MS (ESI) m/z 593.2; MS (ESI) m/z 1185.4; HRMS: calcd for $C_{37}H_{40}N_2O_5$ + H+, 593.30100; found (ESI-FTMS, $[M+H]^{1+}$), 593.30054.

Example 15BB: N-(1,1-dimethyl-2-phenylethyl)-N^2-({4'-[(3-methoxyphenoxy)methyl]biphenyl-4-yl}carbonyl)-L-α-glutamine

[0844] MS (ESI) m/z 595.3; MS (ESI) m/z 1189.6; HRMS: calcd for $C_{36}H_{38}N_2O_6$ + H+, 595.28026; found (ESI-FTMS, $[M+H]^{1+}$), 595.28031.

Example 16: N^2-[(3'-ethoxybiphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0845] The title compound was prepared according to procedures similar to those described in Examples 7 and 11. MS (ESI) m/z 551.2; MS (ESI) m/z 1101.4; MS (ESI) m/z 573.2; HRMS: calcd for $C_{30}H_{34}N_2O_8$ + H+, 551.23879; found (ESI-FTMS, $[M+H]^{1+}$), 551.23735.

[0846] The following compounds were prepared according to procedures similar to those described in Example 16.

Example 17A: N^2-[(2'-ethoxybiphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0847] MS (ESI) m/z 551.2; MS (ESI) m/z 1101.4; MS (ESI) m/z 573.2; HRMS: calcd for $C_{30}H_{34}N_2O_8$ + H+, 551.23879; found (ESI-FTMS, $[M+H]^{1+}$), 551.23739.

Example 17B: N^2-[(4'-methoxybiphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0848] MS (ESI) m/z 537.2; MS (ESI) m/z 1073.4; MS (ESI) m/z 559.2; HRMS: calcd for $C_{29}H_{32}N_2O_8$ + H+, 537.22314; found (ESI-FTMS, $[M+H]^{1+}$), 537.22188.

Example 17C: N^2-[(3'-methoxybiphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0849] HRMS: calcd for $C_{29}H_{32}N_2O_8$ + H+, 537.22314; found (ESI-FTMS, $[M+H]^{1+}$), 537.22188.

Example 17D: 4'-{[((1S)-3-carboxy-1-{[(3,4,5-trimethoxybenzyl)amino]carbonyl}propyl)amino]carbonyl}biphenyl-3-carboxylic acid

[0850] MS (ESI) m/z 551.1; MS (ESI) m/z 1101.3; MS (ESI) m/z 573.1; HRMS: calcd for $C_{29}H_{30}N_2O_9$ + H+, 551.20241; found (ESI-FTMS, $[M+H]^{1+}$), 551.2008.

Example 17E: N^2-[(4'-ethylbiphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0851] MS (ESI) m/z 535.2; MS (ESI) m/z 1069.4; HRMS: calcd for $C_{30}H_{34}N_2O_7$ + H+, 535.24388; found (ESI-FTMS, $[M+H]^{1+}$), 535.2425.

Example 17F: N^2-[(3',4'-dimethoxybiphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0852] MS (ESI) m/z 567.2; MS (ESI) m/z 1133.5; MS (ESI) m/z 589.2; HRMS: calcd for $C_{30}H_{34}N_2O_9$ + H+, 567.23371; found (ESI-FTMS, $[M+H]^{1+}$), 567.23327.

Example 17G: N^2-[(2',4'-dimethoxybiphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0853] MS (ESI) m/z 567.2; MS (ESI) m/z 1133.5; HRMS: calcd for $C_{30}H_{34}N_2O_9$ + H+, 567.23371; found (ESI-FTMS, $[M+H]^{1+}$), 567.23397.

Example 17H: N-(3,4,5-trimethoxybenzyl)-N^2-[(3',4',5'-trimethoxybiphenyl-4-yl)carbonyl]-L-α-glutamine

[0854] MS (ESI) m/z 597.2; MS (ESI) m/z 1193.4; HRMS: calcd for $C_{31}H_{36}N_2O_{10}$ + H+, 597.24427; found (ESI-FTMS, $[M+H]^{1+}$), 597.24385.

Example 17I: N-(1,1-dimethyl-2-phenylethyl)-N^2-[(3'-methoxybiphenyl-4-yl)carbonyl]-L-α-glutamine

[0855] MS (ESI) m/z 489.2; MS (ESI) m/z 977.4; MS (ESI) m/z 511.2; HRMS: calcd for $C_{29}H_{32}N_2O_5$ + H+, 489.23840; found (ESI-FTMS, $[M+H]^{1+}$), 489.2373.

Example 17J: N^2-[(3',4'-dimethoxybiphenyl-4-yl)carbonyl]-N-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0856] MS (ESI) m/z 519.2; MS (ESI) m/z 1037.5; HRMS: calcd for $C_{30}H_{34}N_2O_6$ + H+, 519.24896; found (ESI-FTMS, $[M+H]^{1+}$), 519.248971.

Example 17K: N-(1,1-dimethyl-2-phenylethyl)-N^2-[(2'-ethoxybiphenyl-4-yl)carbonyl]-L-α-glutamine

[0857] MS (ESI) m/z 503.2; MS (ESI) m/z 1005.5; HRMS: calcd for $C_{30}H_{34}N_2O_5$ + H+, 503.25405; found (ESI-FTMS, $[M+H]^{1+}$), 503.25421.

Example 17L: N-(1,1-dimethyl-2-phenylethyl)-N^2-[(3'-fluoro-4'-methylbiphenyl-4-yl)carbonyl]-L-α-glutamine

[0858] MS (ESI) m/z 491.2; MS (ESI) m/z 981.5; HRMS: calcd for $C_{29}H_{31}FN_2O_4$ + H+, 491.23406; found (ESI-FTMS, $[M+H]^{1+}$), 491.23402.

Example 17M: 4-[(4'-Methoxy-3'-methyl-biphenyl-4-carbonyl)-amino]-4-(3,4,5-trimethoxy-benzylcarbamoyl)-butyric acid

[0859] MS (ESI) m/z 551.2; MS (ESI) m/z 1101.5; MS (ESI) m/z 1123.5.

Example 17N: 4-(4-Benzo[1,3]dioxol-5-yl-benzoylamino)-4-(3,4,5-trimethoxy-benzylcarbamoyl)-butyric acid

[0860] MS (ESI) m/z 551.2; MS (ESI) m/z 1101.4.

Example 17O: N-(1-adamantylmethyl)-N^2-[(4'-hydroxybiphenyl-4-yl)carbonyl]-L-α-glutamine

[0861] MS (ESI) m/z 491.4; MS (ESI) m/z 981.7; HRMS: calcd for $C_{29}H_{34}N_2O_5$ + H+, 491.25405; found (ESI-FTMS, $[M+H]^{1+}$), 491.25465.

Example 17P: N^2-[4-(1,3-benzodioxol-5-yl)benzoyl]-N-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0862] MS (ESI) m/z 503.2; MS (ESI) m/z 1005.4; MS (ESI) m/z 525.2; HRMS: calcd for $C_{29}H_{30}N_2O_6$ + H+, 503.21766; found (ESI-FTMS, $[M+H]^{1+}$), 503.21771.

Example 17Q: N^2-[(2',4'-dimethoxybiphenyl-4-yl)carbonyl]-N-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0863] MS (ESI) m/z 519.2; MS (ESI) m/z 1037.5; MS (ESI) m/z 541.2; HRMS: calcd for $C_{30}H_{34}N_2O_6$ + H+, 519.24896; found (ESI-FTMS, $[M+H]^{1+}$), 519.24917.

Example 17R: N^2-[(3'-fluoro-4'-methylbiphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0864] MS (ESI) m/z 539.3; MS (ESI) m/z 1077.6; MS (ESI) m/z 561.3; HRMS: calcd for $C_{29}H_{31}FN_2O_7$ + H+, 539.21881; found (ESI-FTMS, $[M+H]^{1+}$), 539.2182.

Example 17S: N^2-[(4'-sec-butylbiphenyl-4-yl)carbonyl]-N-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0865] MS (ESI) m/z 515.4; MS (ESI) m/z 1029.9; HRMS: calcd for $C_{32}H_{38}N_2O_4$ + H+, 515.29043; found (ESI-FTMS, $[M+H]^{1+}$), 515.29203.

Example 17T: N-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-isopropylbiphenyl-4-yl)carbonyl]-L-α-glutamine

[0866] MS (ESI) m/z 501.4; MS (ESI) m/z 1001.8; HRMS: calcd for $C_{31}H_{36}N_2O_4$ + H+, 501.27478; found (ESI-FTMS, $[M+H]^{1+}$), 501.27468.

Example 17U: N-(1,1-dimethyl-2-phenylethyl)-N^2-(1,1':4',1''-terphenyl-4-ylcarbonyl)-L-α-glutamine

[0867] MS (ESI) m/z 535.4; MS (ESI) m/z 1069.8; HRMS: calcd for $C_{34}H_{34}N_2O_4$ + H+, 535.25913; found (ESI-FTMS, $[M+H]^{1+}$), 535.26044.

Example 17V: N^2-[(4'-hydroxybiphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0868] MS (ESI) m/z 521.3; MS (ESI) m/z 1043.7; HRMS: calcd for $C_{28}H_{30}N_2O_8$ + H+, 523.20749; found (ESI-FTMS, $[M+H]^{1+}$), 523.20878.

Example 17W: N-(1-adamantylmethyl)-N^2-({3'-[(dimethylamino)carbonyl]biphenyl-4-yl}carbonyl)-L-α-glutamine

[0869] MS (ESI) m/z 546.4; MS (ESI) m/z 1091.9; HRMS: calcd for $C_{32}H_{39}N_3O_5$ + H+, 546.29625; found (ESI-FTMS, $[M+H]^{1+}$), 546.29678.

Example 17X: N-(1-adamantylmethyl)-N^2-[(3',5'-dimethylbiphenyl-4-yl)carbonyl]-L-α-glutamine

[0870] MS (ESI) m/z 503.4; MS (ESI) m/z 1005.8; HRMS: calcd for $C_{31}H_{38}N_2O_4$ + H+, 503.29043; found (ESI-FTMS, $[M+H]^{1+}$), 503.29107.

Example 17Y: N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(3'-methylbiphenyl-4-yl)carbonyl]-L-α-glutamine

[0871] MS (ESI) m/z 491.4; MS (ESI) m/z 981.7; MS (ESI) m/z 513.3; HRMS: calcd for $C_{29}H_{31}FN_2O_4$ + H+, 491.23406; found (ESI-FTMS, $[M+H]^{1+}$), 491.23228.

Example 17Z: N^2-[(3'-isopropylbiphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0872] MS (ESI) m/z 549.4; MS (ESI) m/z 1097.9; HRMS: calcd for $C_{31}H_{36}N_2O_7$ + H+, 549.25953; found (ESI-FTMS, $[M+H]^{1+}$), 549.26013.

Example 17AA: N^2-[(4'-isopropylbiphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0873] MS (ESI) m/z 549.4; MS (ESI) m/z 1097.9; HRMS: calcd for $C_{31}H_{36}N_2O_7$ + H+, 549.25953; found (ESI-FTMS, $[M+H]^{1+}$), 549.26066.

Example 17BB: N-(1-adamantylmethyl)-N^2-[4-(1-benzofuran-5-yl)benzoyl]-L-α-glutamine

[0874] MS (ESI) m/z 515.4; MS (ESI) m/z 1029.9; HRMS: calcd for $C_{31}H_{34}N_2O_5$ + H+, 515.25405; found (ESI-FTMS, $[M+H]^{1+}$), 515.25447.

Example 17CC: N-(1-adamantylmethyl)-N^2-[4-(1H-indol-5-yl)benzoyl]-L-α-glutamine

[0875] MS (ESI) m/z 514.4; MS (ESI) m/z 1027.7; HRMS: calcd for $C_{31}H_{35}N_3O_4$ + H+, 514.27003; found (ESI-FTMS, $[M+H]^{1+}$), 514.27038.

Example 17DD: N^2-[(3'-ethoxybiphenyl-4-yl)carbonyl]-N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0876] MS (ESI) m/z 521.4; MS (ESI) m/z 1041.7; HRMS: calcd for $C_{30}H_{33}FN_2O_5$ + H+, 521.24463; found (ESI-FTMS, $[M+H]^{1+}$), 521.24248.

Example 17EE: N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(3'-methoxybiphenyl-4-yl)carbonyl]-L-α-glutamine

[0877] MS (ESI) m/z 507.3; MS (ESI) m/z 1013.7; HRMS: calcd for $C_{29}H_{31}FN_2O_5$ + H+, 507.22898; found (ESI-FTMS, $[M+H]^{1+}$), 507.22717.

Example 17FF: N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(3'-isopropylbiphenyl-4-yl)carbonyl]-L-α-glutamine

[0878] MS (ESI) m/z 519.4; MS (ESI) m/z 1037.7; HRMS: calcd for $C_{31}H_{35}FN_2O_4$ + H+, 519.26536; found (ESI-FTMS, $[M+H]^{1+}$), 519.26474.

Example 17GG: N^2-[(3'-fluoro-4'-methylbiphenyl-4-yl)carbonyl]-N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0879] MS (ESI) m/z 509.3; MS (ESI) m/z 1017.7; HRMS: calcd for $C_{29}H_{30}F_2N_2O_4$ + H+, 509.22464; found (ESI-FTMS, $[M+H]^{1+}$), 509.22537.

Example 17HH: N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(4'-isobutylbiphenyl-4-yl)carbonyl]-L-α-glutamine

[0880] MS (ESI) m/z 533.4; MS (ESI) m/z 1065.8; HRMS: calcd for $C_{32}H_{37}FN_2O_4$ + H+, 533.28101; found (ESI-FTMS, $[M+H]^{1+}$), 533.28214.

Example 17II: N^2-(1,1':4',1''-terphenyl-4-ylcarbonyl)-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0881] MS (ESI) m/z 581.2; MS (ESI) m/z 1163.4; HRMS: calcd for $C_{34}H_{34}N_2O_7$ + H+, 583.24388; found (ESI-FTMS, $[M+H]^{1+}$), 583.24414.

Example 17JJ: N-benzyl-N^2-{[3'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-L-α-glutamine

[0882] MS (ESI) m/z 445.1; MS (ESI) m/z 891.2.

Example 17KK: N-(3,4,5-trimethoxybenzyl)-N^2-[(2',4',6'-trimethylbiphenyl-4-yl)carbonyl]-L-α-glutamine

[0883] HRMS: calcd for $C_{31}H_{36}N_2O_7$ + H+, 549.25953; found (ESI-FTMS, $[M+H]^{1+}$), 549.25817.

Example 17LL: N-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-hydroxybiphenyl-4-yl)carbonyl]-L-α-glutamine

[0884] MS (ESI) m/z 475.2; MS (ESI) m/z 949.4; HRMS: calcd for $C_{28}H_{30}N_2O_5$ + H+, 475.22275; found (ESI-FTMS, $[M+H]^{1+}$), 475.22358.

Example 17MM: N-(1,1-dimethyl-2-phenylethyl)-N^2-[(3'-ethoxybiphenyl-4-yl)carbonyl]-L-α-glutamine

[0885] MS (ESI) m/z 503.2; MS (ESI) m/z 1005.3; MS (ESI) m/z 525.1; HRMS: calcd for $C_{30}H_{34}N_2O_5$ + H+, 503.25405; found (ESI-FTMS, $[M+H]^{1+}$), 503.25252.

Example 17NN: N^2-[4-(1,3-benzodioxol-5-yl)benzoyl]-N-(3-methylbenzyl)-L-α-glutamine

[0886] MS (ESI) m/z 475.1; MS (ESI) m/z 949.2; HRMS: calcd for $C_{27}H_{26}N_2O_6$ + H+, 475.18636; found (ESI-FTMS, $[M+H]^{1+}$), 475.1872.

Example 17OO: N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(4'-hydroxybiphenyl-4-yl)carbonyl]-L-α-glutamine

[0887] MS (ESI) m/z 493.2; MS (ESI) m/z 985.4; HRMS: calcd for $C_{28}H_{29}FN_2O_5$ + H+, 493.21333; found (ESI-FTMS, $[M+H]^{1+}$), 493.21327.

Example 17PP: N^2-[4-(1,3-benzodioxol-5-yl)benzoyl]-N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine

[0888] (1): MS (ESI) m/z 521.1; MS (ESI) m/z 1041.3; HRMS: calcd for $C_{29}H_{29}FN_2O_6$ + H+, 521.20824; found (ESI-FTMS, $[M+H]^{1+}$), 521.20872; (2): MS (ESI) m/z 521.2;
MS (ESI) m/z 1041.3.

Example 17QQ: N-benzyl-N^2-{4-[(4-hydroxycyclohexyl)ethynyl]benzoyl}-L-α-glutamine

[0889] MS (ESI) m/z 463.1; MS (ESI) m/z 925.3.

Example 17RR: N^2-[(3'-hydroxybiphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0890] HRMS: calcd for $C_{28}H_{30}N_2O_8$ + H+, 523.20749; found (ESI-FTMS, $[M+H]^{1+}$), 523.20809.

Example 17SS: N-(1,1-dimethyl-2-phenylethyl)-N^2-{[4'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-L-α-glutamine

[0891] MS (ESI) m/z 487.1; MS (ESI) m/z 975.2; HRMS: calcd for $C_{29}H_{32}N_2O_5$ + H+, 489.23840; found (ESI-FTMS, $[M+H]^{1+}$), 489.2389.

Example 17TT: N-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-methylbiphenyl-4-yl)carbonyl]-L-α-glutamine

[0892] MS (ESI) m/z 473.1; MS (ESI) m/z 945.3; HRMS: calcd for $C_{29}H_{32}N_2O_4$ + H+, 473.24348; found (ESI-FTMS, $[M+H]^{1+}$), 473.24409.

Example 17UU: N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(3'-hydroxybiphenyl-4-yl)carbonyl]-L-α-glutamine

[0893] MS (ESI) m/z 493.2; MS (ESI) m/z 985.4.

Example 17VV: N^1-benzyl-N^2-(4-pyridin-4-ylbenzoyl)-L-α-glutamine

[0894] MS (ESI) m/z 418.2; HRMS: calcd for $C_{24}H_{23}N_3O_4$ + H+, 418.17613; found (ESI_FT, $[M+H]^{1+}$), 418.17461.

Example 17WW: N^1-benzyl-N^2-(1,1'-biphenyl-3-ylcarbonyl)-L-α-glutamine

[0895] MS (ESI) m/z 417.1; MS (ESI) m/z 833.1; HRMS: calcd for $C_{25}H_{24}N_2O_4$ + H+, 417.18088; found (ESI-FTMS, $[M+H]^{1+}$), 417.18049.

Example 17XX: N^1-benzyl-N^2-(3-thien-2-ylbenzoyl)-L-α-glutamine

[0896] MS (ESI) m/z 423.1; MS (ESI) m/z 845; HRMS: calcd for $C_{23}H_{22}N_2O_4S$ + H+, 423.13730; found (ESI-FTMS, $[M+H]^{1+}$), 423.1383.

Example 17YY: N^1-benzyl-N^2-[(3-chloro-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0897] MS (ESI) m/z 451.1; MS (ESI) m/z 901; HRMS: calcd for $C_{25}H_{23}ClN_2O_4$ + H+, 451.14191; found (ESI-FTMS, $[M+H]^{1+}$), 451.1417.

Example 17ZZ: N^1-benzyl-N^2-[(3-fluoro-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0898] HRMS: calcd for $C_{25}H_{23}FN_2O_4$ + H+, 435.17146; found (ESI-FTMS, $[M+H]^{1+}$), 435.17091.

Example 17AAA: N^1-benzyl-N^2-[(2,6-dimethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine

[0899] HRMS: calcd for $C_{27}H_{28}N_2O_6$ + H+, 477.20201; found (ESI-FTMS, $[M+H]^{1+}$), 477.20098.

Example 17BBB: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methoxy-1,1'-biphenyl-3-yl)-L-α-glutamine

[0900] MS (ESI) m/z 509.2; MS (ESI) m/z 1017.2; HRMS: calcd for $C_{31}H_{28}N_2O_5$ + H+, 509.20710; found (ESI-FTMS, $[M+H]^{1+}$), 509.20875.

Example 18: N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0901] MS (ESI) m/z 673.4; MS (ESI) m/z 1345.9; HRMS: calcd for $C_{37}H_{40}N_2O_{10}$ + H+, 673.27557; found (ESI-FTMS, $[M+H]^{1+}$), 673.27498.

Example 19:

[0902] The following compounds were prepared according to procedures similar to those described in Example 18.

Example 19A: N-(1-adamantylmethyl)-N^2-({4'-[(3-methoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutamine

[0903] MS (ESI) m/z 611.5; MS (ESI) m/z 1222; HRMS: calcd for $C_{37}H_{42}N_2O_6$ + H+, 611.31156; found (ESI-FTMS, $[M+H]^{1+}$), 611.31164.

Example 19B: N-(1-adamantylmethyl)-N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutamine

[0904] MS (ESI) m/z 641.5; MS (ESI) m/z 1282; HRMS: calcd for $C_{38}H_{44}N_2O_7$ + H+, 641.32213; found (ESI-FTMS, $[M+H]^{1+}$), 641.32171.

Example 19C: N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-N-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0905] MS (ESI) m/z 625.5; MS (ESI) m/z 1249.9; HRMS: calcd for $C_{37}H_{40}N_2O_7$ + H+, 625.29083; found (ESI-FTMS, $[M+H]^{1+}$), 625.2906.

Example 19D: N^2-({4'-[(3,5-dimethylbenzyl)oxy]biphenyl-4-yl}carbonyl)-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0906] MS (ESI) m/z 641.5; MS (ESI) m/z 1282.

Example 19E: N^2-[(4'-{[3,5-bis(trifluoromethyl)benzyl]oxy}biphenyl-4-yl)carbonyl]-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0907] MS (ESI) m/z 749.5; MS (ESI) m/z 771.5; HRMS: calcd for $C_{37}H_{34}F_6N_2O_8$ + H+, 749.22921; found (ESI-FTMS, $[M+H]^{1+}$), 749.2297.

Example 19F: N-(1,1-dimethyl-2-phenylethyl)-N^2-({4'-[(3-methoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutamine

[0908] MS (ESI) m/z 595.3; MS (ESI) m/z 1189.5; HRMS: calcd for $C_{36}H_{38}N_2O_6$ + H+, 595.28026; found (ESI-FTMS, $[M+H]^{1+}$), 595.28185.

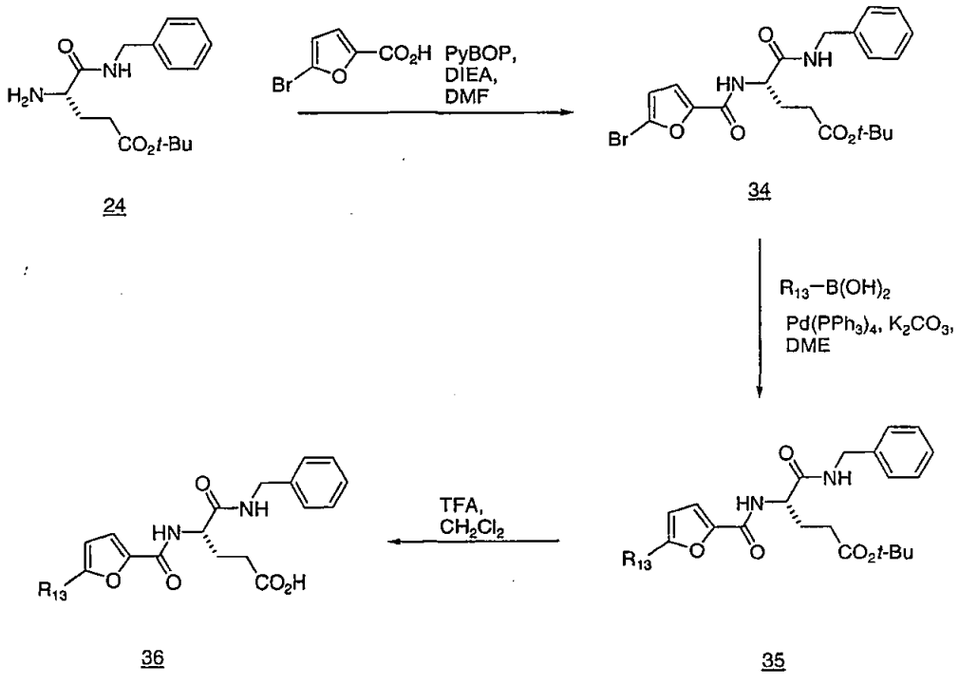
Example 19G: N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-N-(6-hydroxyhexyl)-L-α-glutamine

[0909] MS (ESI) m/z 591.2; HRMS: calcd for $C_{33}H_{40}N_2O_8$ + H+, 593.28574; found (ESI-FTMS, $[M+H]^{1+}$), 593.28726.

Example 19H: N^2-({4'-[(3-methoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0910] MS (ESI-FTMS) m/z 643.26499; MS (ESI-FTMS) m/z 643.26501; HRMS: calcd for $C_{36}H_{38}N_2O_9$ + H+, 643.26501; found (ESI-FTMS, $[M+H]^{1+}$), 643.26499.

Scheme 11



Example 20: N^1-benzyl-N^2-(5-phenyl-2-furoyl)-L-α-glutamine

[0911] Step A: *tert*-butyl N^1-benzyl-N^2-(5-bromo-2-furoyl)-L-α-glutaminate

Tert-butyl N^1-benzyl-L-α-glutaminate (2.33g, 7.98mmol) was dissolved in DMF (7mL) under nitrogen. 5-Bromofuroic acid (1.52g, 7.98mmol) was added, followed by addition of PyBOP (5.00g, 9.6mmol). Finally, DIEA (1.67mL, 9.6mmol) was added dropwise over 5 minutes via addition funnel. The reaction was monitored by TLC and stirred overnight. The solution was diluted with EtOAc (250 mL), washed consecutively with H_2O, 10% HCl, saturated $NaHCO_3$, brine, and then dried over Na_2SO_4. After solvent was evaporated, the crude residue was dissolved in ether and washed with aq. LiBr (2 x 250 mL) and dried over Na_2SO_4. Ether was removed, leaving an oil which was further purified on a SiO_2 column using 33%-40%EtOAc/Hex as the solvent. The product was

the third spot off the column and a sticky orange solid. Yield 1.60g of *tert*-butyl N^1-benzyl-N^2-(5-bromo-2-furoyl)-L-α-glutaminate at 43% yield.

[0912] Step B: *tert*-butyl N^1-benzyl-N^2-(5-phenyl-2-furoyl)-L-α-glutaminate

HRMS: calcd for $C_{27}H_{30}N_2O_5$ + Na+, 485.20469; found (ESI_FTMS, $[M+Na]^{1+}$), 485.20466.

[0913] Step C: N^1-benzyl-N^2-(5-phenyl-2-furoyl)-L-α-glutamine

HRMS: calcd for $C_{23}H_{22}N_2O_5$ + H+, 407.16015; found (ESI_FTMS, $[M+H]^{1+}$), 407.15841.

Example 21:

[0914] The following compounds were prepared according to procedures similar to those described in Example 20.

Example 21A: N^1-benzyl-N^2-[5-(3-ethoxyphenyl)-2-furoyl]-L-α-glutamine

[0915] Step B: *tert*-butyl N^1-benzyl-N^2-[5-(3-ethoxyphenyl)-2-furoyl]-L-α-glutaminate

HRMS: calcd for $C_{29}H_{34}N_2O_6$ + H+, 507.24896; found (ESI_FTMS, $[M+H]^{1+}$), 507.24894.

[0916] Step C: N^1-benzyl-N^2-[5-(3-ethoxyphenyl)-2-furoyl]-L-α-glutamine

HRMS: calcd for $C_{25}H_{26}N_2O_6$ + H+, 451.18636; found (ESI_FTMS, $[M+H]^{1+}$), 451.18545.

Example 21B: N^1-benzyl-N^2-[5-(3,5-dimethylphenyl)-2-furoyl]-L-α-glutamine

[0917] Step B: *tert*-butyl N^1-benzyl-N^2-[5-(3,5-dimethylphenyl)-2-furoyl]-L-α-glutaminate

HRMS: calcd for $C_{29}H_{34}N_2O_5$ + H+, 491.25405; found (ESI_FTMS, $[M+H]^{1+}$), 491.2538.

[0918] Step C: N^1-benzyl-N^2-[5-(3,5-dimethylphenyl)-2-furoyl]-L-α-glutamine

HRMS: calcd for $C_{25}H_{26}N_2O_5$ + H+, 435.19145; found (ESI_FTMS, $[M+H]^{1+}$), 435.19034.

Example 21C: N^1-benzyl-N^2-(2,2'-bifuran-5-ylcarbonyl)-L-α-glutamine

[0919] Step B: *tert*-butyl N^1-benzyl-N^2-(2,2'-bifuran-5-ylcarbonyl)-L-α-glutaminate

HRMS: calcd for $C_{25}H_{28}N_2O_6$ + H+, 453.20201; found (ESI_FTMS, $[M+H]^{1+}$), 453.20173.

[0920] Step C: N^1-benzyl-N^2-(2,2'-bifuran-5-ylcarbonyl)-L-α-glutamine

HRMS: calcd for $C_{21}H_{20}N_2O_6$ + H+, 397.13941; found (ESI_FTMS, $[M+H]^{1+}$), 397.13777.

Example 21D: N^1-benzyl-N^2-(5-thien-2-yl-2-furoyl)-L-α-glutamine

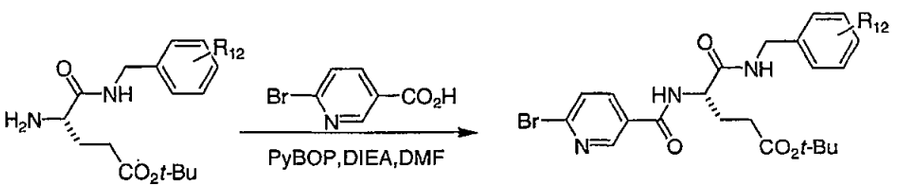
[0921] Step B: *tert*-butyl N^1-benzyl-N^2-(5-thien-2-yl-2-furoyl)-L-α-glutaminate

HRMS: calcd for $C_{25}H_{28}N_2O_5S$ + H+, 469.17917; found (ESI_FTMS, $[M+H]^{1+}$), 469.1789.

[0922] Step C: N^1-benzyl-N^2-(5-thien-2-yl-2-furoyl)-L-α-glutamine

HRMS: calcd for $C_{21}H_{20}N_2O_5S$ + H+, 413.11657; found (ESI_FTMS, $[M+H]^{1+}$), 413.11511.

Scheme 12



37 38

Example 22:

[0923] The following compounds were prepared according to procedures similar to those described in Example 20.

Example 22A: N^1-benzyl-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine

[0924] Step A: *tert*-butyl N^1-benzyl-N^2-[(6-bromopyridin-3-yl)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 476.1; MS (ESI) *m/z* 951.1; HRMS: calcd for $C_{22}H_{26}BrN_3O_4$ + H+, 476.11794; found (ESI-FTMS, $[M+H]^{1+}$), 476.11935.

[0925] Step B: *tert*-butyl N^1-benzyl-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 474.2; HRMS: calcd for $C_{28}H_{31}N_3O_4$ + H+, 474.23873; found (ESI-FTMS, $[M+H]^{1+}$), 474.23861.

[0926] Step C: N^1-benzyl-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine

MS (ESI) *m/z* 418.1; HRMS: calcd for $C_{24}H_{23}N_3O_4$ + H+, 418.17613; found (ESI-FTMS, $[M+H]^{1+}$), 418.17674.

Example 22B: N^1-(3-methoxybenzyl)-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine

[0927] Step A: *tert*-butyl N^2-[(6-bromopyridin-3-yl)carbonyl]-N^1-(3-methoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 506.1; MS (ESI) *m/z* 1011.1; HRMS: calcd for $C_{23}H_{28}BrN_3O_5$ + H+, 506.12851; found (ESI-FTMS, $[M+H]^{1+}$), 506.12839.

[0928] Step B: *tert*-butyl N^1-(3-methoxybenzyl)-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutaminate

MS (ESI) *m/z* 504.2; HRMS: calcd for $C_{29}H_{33}N_3O_5$ + H+, 504.24930; found (ESI-FTMS, $[M+H]^{1+}$), 504.24835.

[0929] Step C: N^1-(3-methoxybenzyl)-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine

MS (ESI) *m/z* 448.1; HRMS: calcd for $C_{25}H_{25}N_3O_5$ + H+, 448.18670; found (ESI-FTMS, $[M+H]^{1+}$), 448.18686.

Example 22C: N^2-[(2,2'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-N^1-(3-methoxybenzyl)-L-α-glutamine

[0930] Step B: *tert*-butyl N^2-[(2,2'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-N^1-(3-methoxybenzyl)-L-α-glutaminate

MS (ESI) *m/z* 531.3; MS (ESI) *m/z* 1061.4; HRMS: calcd for $C_{32}H_{38}N_2O_5$ + H+, 531.28535; found (ESI_FTMS, $[M+H]^{1+}$), 531.2855.

[0931] Step C: N^2-[(2,2'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-N^1-(3-methoxybenzyl)-L-α-glutamine

HRMS: calcd for $C_{28}H_{30}N_2O_5$ + H+, 475.22275; found (ESI_FTMS, $[M+H]^{1+}$), 475.22271.

Example 22D: N^2-(4-bromobenzoyl)-N-(3,4,5-trimethoxybenzyl)-L-α-glutamine

[0932] MS (ESI) m/z 507; MS (ESI) m/z 1015.1; HRMS: calcd for $C_{22}H_{25}BrN_2O_7$ + H+, 509.09179; found (ESI-FTMS, $[M+H]^{1+}$), 509.09078.

Example 22E: N^2-(4-bromobenzoyl)-N-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine

[0933] MS (ESI) m/z 461.1; MS (ESI) m/z 921.2; HRMS: calcd for $C_{22}H_{25}BrN_2O_4$ + H+, 461.10705; found (ESI-FTMS, $[M+H]^{1+}$), 461.10805.

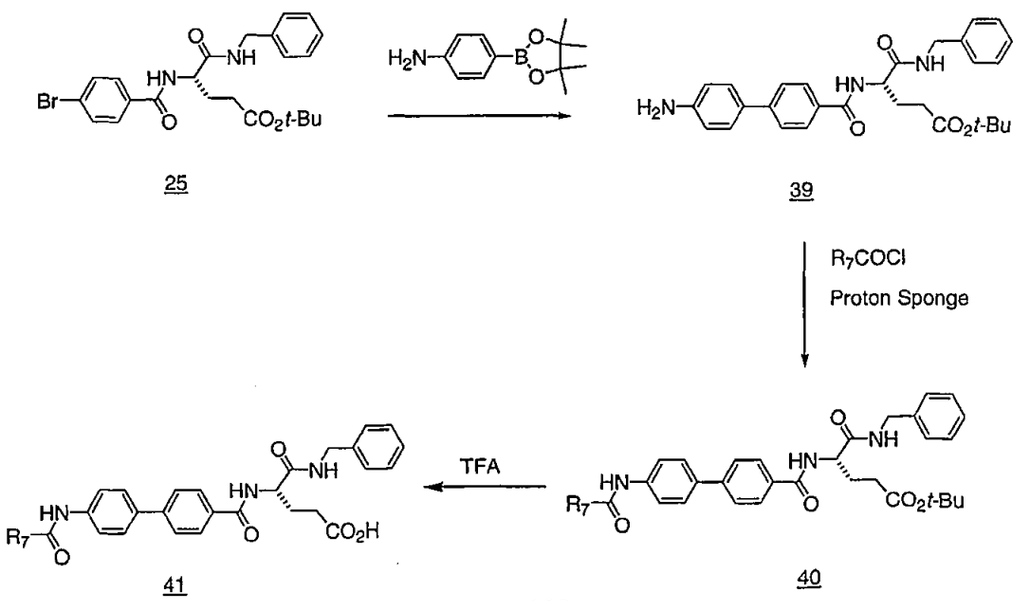
Example 22F: N-(1-adamantylmethyl)-N^2-(4-bromobenzoyl)-L-α-glutamine

[0934] MS (ESI) m/z 477.3; MS (ESI) m/z 953.5; HRMS: calcd for $C_{23}H_{29}BrN_2O_4$ + H+, 477.13835; found (ESI-FTMS, $[M+H]^{1+}$), 477.13801.

Example 22G: N^2-(4-bromobenzoyl)-N-(3-methylbenzyl)-L-α-glutamine

[0935] MS (ESI-FTMS) m/z 433.07562; MS (ESI-FTMS) m/z 433.07575; HRMS: calcd for $C_{20}H_{21}BrN_2O_4$ + H+, 433.07575; found (ESI-FTMS, $[M+H]^{1+}$), 433.07562.

Scheme 13



Example 23: N^2-{[4'-(acetylamino)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutamine

[0936] Step A: *tert*-butyl N^2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]-N^1-benzyl-L-α-glutaminate

4-Benzylcarbamoyl-4-(4-bromo-benzoylamino)-butyric acid tert-butyl ester (3.0 g, 6.31 mmol, 1 equiv.) was dissolved in DME (60 mL) was added to 4-(4,4,5,5,)-tetramethyl-1,3,2-dioxoborolan-2-yl)aniline (1.38 g, 6.31 mmol, 1 equiv.) and $Pd(PPh_3)_4$ (728 mg, 0.063 mmol, 0.1 equiv.). The mixture was stirred for 30 minutes prior to the addition of aq. K_2CO_3 (1.74 g, 12.6 mmol, 2 equiv.) in 12 mL H_2O. The mixture was capped in a sealed vessel and stirred overnight at 80°C. The reaction was complete as determined by TLC. The mixture was filtered over celite, the solvent was removed, and the resulting tan solid was diluted with EtOAc (200 mL) and washed consecutively with H_2O, 10% HCl, and brine, and then dried over Na_2SO_4. The solid was purified by column chromatography (silica gel, 41% Acetone/Hexanes) to give 1.89 g of *tert*-butyl N^2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]-N^1-benzyl-L-α-glutaminate in 61% yield. MS (ESI) *m/z* 488.2; HRMS: calcd for $C_{29}H_{33}N_3O_4$ + H+, 488.25438; found (ESI_FTMS, $[M+H]^{1+}$), 488.25433.

[0937] Step B: isopropyl N^2-{[4'-(acetylamino)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutaminate

4-[(4'-Amino-biphenyl-4-carbonyl)-amino]-4-benzylcarbamoyl-butyric acid tert-butyl ester (300 mg, 0.62 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C followed by the addition of proton sponge (266 mg, 1.24 mmol, 2 equiv.). The mixture was stirred 30 minutes prior to the addition of acetyl chloride (48 μL, 0.68 mmol, 1.1 equiv.) The mixture was stirred at 0°C for 1.5 hrs and allowed to warm to room temperature. Reaction was complete as determined by TLC. The mixture was washed consecutively with H_2O, $NaHCO_3$ satd., and brine, and then dried over Na_2SO_4. The tan solid was purified by preparative HPLC to give 85 mg of isopropyl N^2-{[4'-(acetylamino)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutaminate in 26% yield. MS (ESI) *m/z* 557.2; MS (ESI) *m/z* 279.1.

[0938] Step C: N^2-{[4'-(acetylamino)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutamine

4-[(4'-Acetylamino-biphenyl-4-carbonyl)-amino]-4-benzylcarbamoyl-butyric acid tert-

butyl ester (75 mg) was dissolved in dichloroethane (4 mL) and added to TFA (2 mL). The mixture was stirred at room temperature for 3 hrs. Reaction was complete as determined by TLC. The solvent was removed and the resulting solid was purified by preparative HPLC to give N^2-{[4'-(acetylamino)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutamine in 54% yield (37 mg).

MS (ESI) *m/z* 474.2; MS (ESI) *m/z* 947.3; HRMS: calcd for $C_{27}H_{27}N_3O_5$ + H+, 474.20235; found (ESI_FTMS, $[M+H]^{1+}$), 474.20274.

Example 24:

[0939] The following compounds were prepared according to procedures similar to those described in Example 23.

Example 24A: N^1-benzyl-N^2-{[4'-(2-furoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine

[0940] Step B: *tert*-butyl N^1-benzyl-N^2-{[4'-(2-furoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutaminate

MS (ESI) *m/z* 582.3; MS (ESI) *m/z* 1163.5; HRMS: calcd for $C_{34}H_{35}N_3O_6$ + H+, 582.25986; found (ESI_FTMS, $[M+H]^{1+}$), 582.26058.

[0941] Step C: N^1-benzyl-N^2-{[4'-(2-furoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine

MS (ESI) *m/z* 526.2; MS (ESI) *m/z* 1051.3; HRMS: calcd for $C_{30}H_{27}N_3O_6$ + H+, 526.19726; found (ESI_FTMS, $[M+H]^{1+}$), 526.19773.

Example 24B: N^1-benzyl-N^2-({4'-[(4-fluorobenzoyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutamine

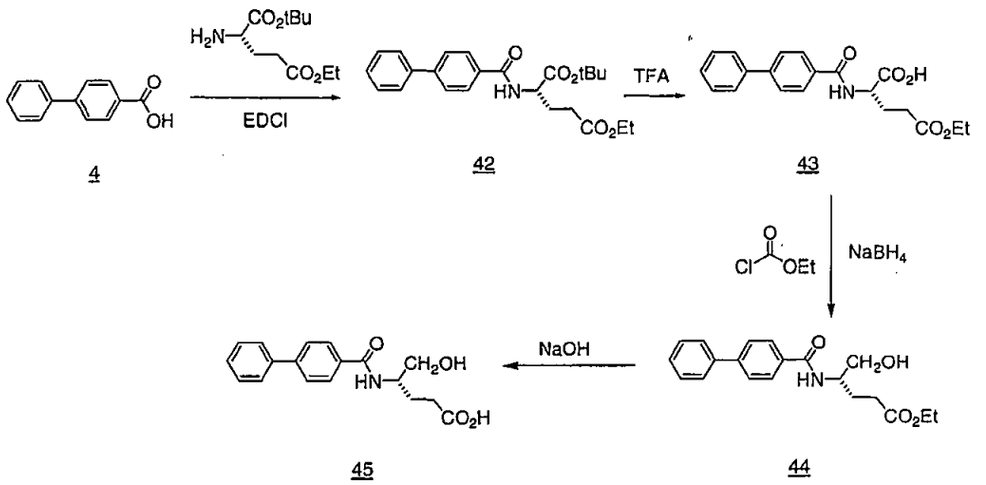
[0942] Step B: *tert*-butyl N^1-benzyl-N^2-({4'-[(4-fluorobenzoyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutaminate

[0943] Step C: N^1-benzyl-N^2-({4'-[(4-fluorobenzoyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutamine

Example 24C: N^2-{[4'-(benzoylamino)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutamine

[0944] HRMS: calcd for $C_{32}H_{29}N_3O_5$ - H+, 534.20345; found (ESI_FTMS, $[M-H]^{1-}$), 534.2024.

Scheme 14



Example 25: 4-[(Biphenyl-4-carbonyl)-amino]-5-hydroxy-pentanoic acid

[0945] Step A: 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid 1-tert-butyl ester 5-methyl ester

4-Diphenyl carboxylic acid (3.57 g, 18 mmol) and EDCI (4.28 g, 22.3 mmol, 1.2 equiv.) were dissolved in DMF (40 mL). The mixture was stirred at room temperature for 0.5 hrs. H-Glu(OMe)OtBu (5.02 g, 19.8 mmol, 1.1 equiv.) was added, followed by the addition of Et_3N (6.77 mL, 48.6 mmol, 2.7 equiv.) and DMAP (330 mg, 2.7 mmol, 15%). The mixture was stirred overnight under N_2. The reaction mixture was then diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over $MgSO_4$, concentrated, and purified by column chromatography (20% EtOAc / Hexane) to afford 3.2 g of 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid 1-tert-butyl ester 5-methyl ester in 44.7% yield. MS (ESI) *m/z* 396.

[0946] Step B: 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid 5-methyl ester 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid 1-tert-butyl ester 5-methyl ester (1.5 g, 3.8 mmol) was dissolved in dichloroethane (26 mL) and the mixture was added to TFA (13 mL). The mixture was stirred at room temperature for 4 hrs. TLC indicated the reaction was complete. Solvent was evaporated by rotovap. The solid obtained was washed with EtOAc and water. After drying, 2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid 5-methyl ester was obtained in 87% yield (1.128 g). MS (ESI) *m/z* 342.

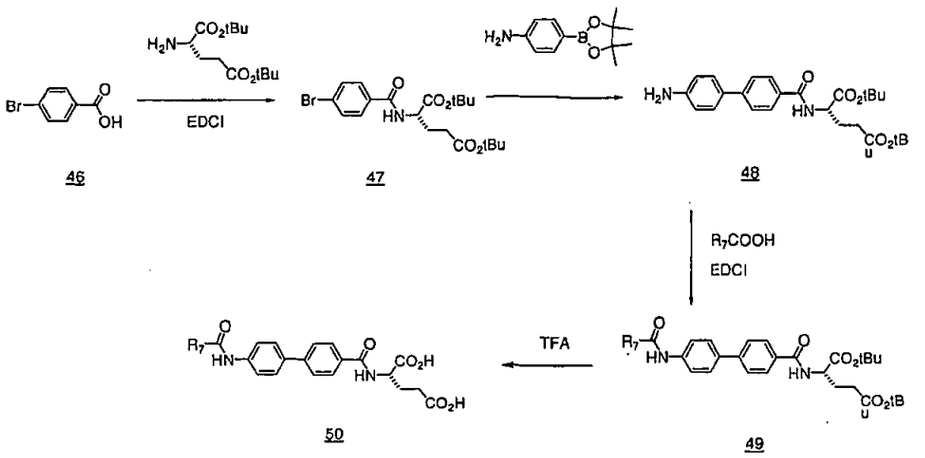
[0947] Step C: 4-[(Biphenyl-4-carbonyl)-amino]-5-hydroxy-pentanoic acid methyl ester

2-[(Biphenyl-4-carbonyl)-amino]-pentanedioic acid 5-methyl ester (1.128g, 3.30mmol, 1.0 equiv.) was dissolved in THF (35 mL). The mixture was cooled to –20°C, followed by the addition of Et_3N (343 mg, 3.3 mmol, 1.0 equiv.) and ethyl chloroformate (358 mg, 3.3 mmol, 1.0 equiv.). After stirring for 20 minutes, $NaBH_4$ (375 mg, 9.9 mmol, 3 equiv.) was added and the temperature was raised to –10°C. After stirring for 5 min, MeOH (30mL) was introduced and the mixture was further stirred for 20 min at this temperature and then at 0°C for 20 min. 1N HCl was then added slowly to quench the reaction. Solvent was evaporated and the residue partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, and removed solvent by rotavap. The crude mixture was then purified by column chromatography (silica gel, 3 % MeOH / CH_2Cl_2) to afford 333 mg of 4-[(Biphenyl-4-carbonyl)-amino]-5-hydroxy-pentanoic acid methyl ester in 31 % yield. MS (ESI) *m/z* 328.

[0948] Step D: 4-[(Biphenyl-4-carbonyl)-amino]-5-hydroxy-pentanoic acid

A solution of 4-[(Biphenyl-4-carbonyl)-amino]-5-hydroxy-pentanoic acid methyl ester (333 mg, 1.06 mmol) in THF (10 mL) and MeOH (1.27 mL) was added to 1N NaOH (1.27 mL, 1.27 mmol, 1.2 equiv) at room temperature. The mixture was stirred for 2 hours and TLC indicated the reaction was complete. Solvent was removed and the residue was dissolved in water. After adjusting the pH to 4 with 1N HCl, solid precipitated from the solution. The solid was then collected by filtration, washed with water, and dried under vacuum overnight to afford 240 mg of 4-[(Biphenyl-4-carbonyl)-amino]-5-hydroxy-pentanoic acid in 76.7% yield. MS (ESI) *m/z* 314.

Scheme 15



Example 26: N-({4'-[(phenylacetyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-glutamic acid

[0949] Step A: 2-(4-Bromo-benzoylamino)-pentanedioic acid di-tert-butyl ester A solution of 4-Bromobenzoic acid (4 g, 19.9 mmol, 1 equiv) in DMF (140 mL) was added to EDCI (5.72 g, 29.8 mmol, 1.5 equiv.) and the mixture was stirred at room temperature for 25 min. Et_3N (6.9 mL, 49.7 mmol, 2.5 equiv) was then added, followed by addition of DMAP (486 mg, 4.0 mmol, 20%). The reaction mixture was allowed to stir at room temperature overnight. Reaction was complete as determined by TLC. DMF was removed by rotavap and the residue partitioned between EtOAc and brine solution. The organic layer was separated, dried over $MgSO_4$ and concentrated. The crude mixture was purified by column chromatography (silica gel, 20% EtOAc / Hexane) to give 4.2 g of 2-(4-Bromo-benzoylamino)-pentanedioic acid di-tert-butyl ester in 47.7% yield. MS (ESI) *m/z* 441.

[0950] Step B: 2-[(4'-Amino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester

4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (1.34g, 6.104 mmol, 1 equiv.) and 2-(4-Bromo-benzoylamino)-pentanedioic acid di-tert-butyl ester (2.7g, 6.104 mmol, 1 equiv.) were dissolved in DME (120 mL). A solution of K_2CO_3 (1.68 g, 12.21 mmol, 2 equiv.) in 30 mL of water was injected into the mixture, followed by the addition of $Pd(PPh_3)_4$ (352 mg, 0.31 mmol, 5%). The mixture was heated to reflux overnight. Reaction was complete as determined by TLC. Regular work-up and column chromatography (silica gel, 30-40% EtOAc / n-Hexane) afforded 2.3 g of 2-[(4'-Amino-

biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester in 83 % yield. MS (ESI) *m/z* 453.

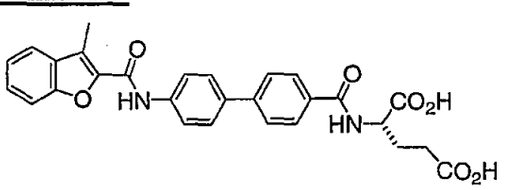
[0951] Step C: Phenylacetylamino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester

A solution of phenylacetic acid (89 mg, 0.65 mmol, 1 equiv) in DMF (10 mL) was added to EDCI (188 mg, 0.98 mmol, 1.5 equiv.). After stirring for 20 min, 2-[(4'-Amino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester (297 mg, 0.65 mmol, 1 equiv.) was added, followed by the addition of Et_3N (0.23 mL, 1.64 mmol, 2.5 equiv.) and DMAP (16 mg, 0.13 mmol, 20%). The reaction mixture was allowed to stir at room temperature overnight. Reaction was complete as determined by TLC. DMF was removed and the residue was dissolved in EtOAc. The organic layer was washed with H_2O and brine, and then dried over $MgSO_4$. After solvent was evaporated, the crude residue was purified by HPLC to give 45 mg of 2-[(4'-Phenylacetylamino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester in 12 % yield. MS (ESI) *m/z* 573.

[0952] Step D: N-({4'-[(phenylacetyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-glutamic acid

2-[(4'-Phenylacetylamino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester (45 mg) was dissolved in dichloroethane (3 mL) and added to TFA (1 mL). The mixture was stirred at room temperature for 3 hrs. Reaction was complete as determined by TLC. Solvent was removed and the resulting solid was dried under vacuum overnight. N-({4'[(phenylacetyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-glutamic acid was obtained in 84.2% yield (30.3 mg). MS (ESI) *m/z* 461.

Example 27: N-[(4'-{[(3-Methyl-1-benzofuran-2-yl)carbonyl]-amino}-1,1'-biphenyl-4-yl)carbonyl]-L-glutamic acid



[0953] The title compound was prepared according to procedures similar to those described in Example 26.

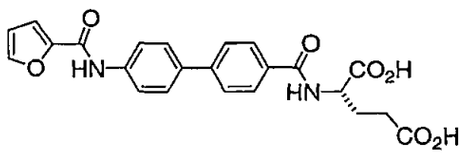
[0954] Step C: 2-({4'-[(3-Methyl-benzofuran-2-carbonyl)-amino]-biphenyl-4-carbonyl}-amino)-pentanedioic acid di-tert-butyl ester

EDCI coupling between 3-Methylbenzofuran 2 carboxylic acid (139 mg, 0.79 mmol) and 2-[(4'-Amino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester (358 mg, 0.79 mmol, 1 equiv.) was carried out according to the procedure in step C of Example 5 to give 2-({4'-[(3-Methyl-benzofuran-2-carbonyl)-amino]-biphenyl-4-carbonyl}-amino)-pentanedioic acid di-tert-butyl ester in 12.4% yield (60 mg). MS (ESI) *m/z* 611.

[0955] Step D: N-[(4'-{[(3-Methyl-1-benzofuran-2-yl)carbonyl]-amino}-1,1'-biphenyl-4-yl)carbonyl]-L-glutamic acid

Hydrolysis of 2-({4'-[(3-Methyl-benzofuran-2-carbonyl)-amino]-biphenyl-4-carbonyl}-amino)-pentanedioic acid di-tert-butyl ester (60 mg) was carried out according to procedure in step D of Example 5 to give N-[(4'-{[(3-Methyl-1-benzofuran-2-yl)carbonyl]-amino}-1,1'-biphenyl-4-yl)carbonyl]-L-glutamic acid in 59 % yield (28.9 mg). MS (ESI) *m/z* 499.

Example 28: N-{[4'-(2-furoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid



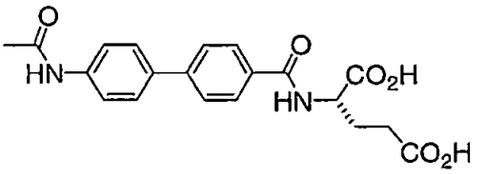
[0956] Step A: 2-({4'-[(Furan-2-carbonyl)-amino]-biphenyl-4-carbonyl}-amino)-pentanedioic acid di-tert-butyl ester

To a solution of 2-[(4'-Amino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester (350 mg, 0.77 mmol) and 2-Furoic acid (87 mg, 0.77 mmol, 1 equiv.) in DMF (6 mL) was added BOP reagent (409 mg, 0.92 mmol, 1.2 equiv.) and Hunig base (0.16 mL, 0.92 mmol, 1.2 equiv.) under N_2. The mixture was stirred at room temperature overnight. Reaction was complete was determined by LC-MS. The reaction mixture was then poured onto cold water. Solid precipitated from the mixture was collected by filtration. The solid was then dissolved in EtOAc, washed with 1N HCl, saturated $NaHCO_3$, and brine, and then dried over $MgSO_4$. After removing the solvent, the solid was dried under vacuum overnight to provide 2-({4'-[(Furan-2-carbonyl)-amino]-biphenyl-4-carbonyl}-amino)-pentanedioic acid di-tert-butyl ester in 87 % yield (369 mg). MS (ESI) *m/z* 549.

[0957] Step B: N-{[4'-(2-furoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid

2-({4'-[(Furan-2-carbonyl)-amino]-biphenyl-4-carbonyl}-amino)-pentanedioic acid di-tert-butyl ester (369 mg, 0.67 mmol) was dissolved in dichloroethane (10 mL) and added to TFA (5mL) at 0 °C. The cooling bath was removed after the addition was complete. The mixture was stirred at room temperature for 3 hrs. and the reaction was complete as determined by TLC. After removing solvent, the residue was washed 3 times with EtOAc. The solid was then dried under vacuum to give 2-({4'-[(Furan-2-carbonyl)-amino]-biphenyl-4-carbonyl}-amino)-pentanedioic acid in 85.6% yield (251 mg). MS (ESI) *m/z* 437.

Example 29: N-{[4'-(acetylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid



[0958] The title compound was prepared according to procedures similar to those described in Example 28.

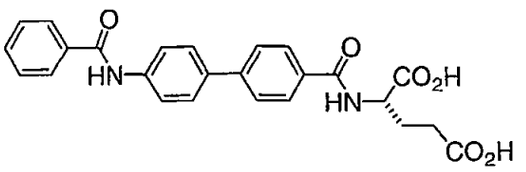
[0959] Step A: 2-[(4'-Acetylamino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester

BOP coupling of 2-[(4'-Amino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester (350 mg, 0.77 mmol) was carried out according to procedures in step A of Example 6B to give 344 mg of 2-[(4'-Acetylamino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester in 89% yield. MS (ESI) *m/z* 497.

[0960] Step B: N-{[4'-(acetylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid

Hydrolysis of 2-[(4'-Acetylamino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester (344 mg, 0.69 mmol) was carried out according to procedures in step B for Example 6B to give 212 mg of 2-[(4'-Acetylamino-biphenyl-4-carbonyl)-amino]-pentanedioic acid in 79.7% yield. MS (ESI) *m/z* 383.

Example 30: N-{[4'-(benzoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid

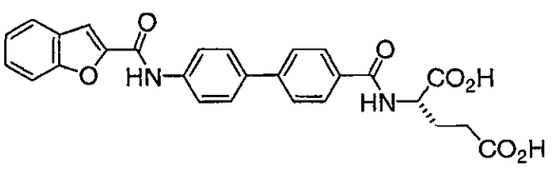


[0961] The title compound was prepared according to procedures similar to those described for Example 6B.

[0962] Step D: N-{[4'-(benzoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid

Hydrolysis of 2-[(4'-Benzoylamino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester (191 mg) was carried out according to procedures in step D of Example 6B to give N-{[4'-(benzoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid in 61.6% yield (93.7 mg). MS (ESI) *m/z* 445.

Example 31: N-({4'-[(1-benzofuran-2-ylcarbonyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-glutamic acid



[0963] The title compound was prepared according to the procedures similar to that described for Example 28.

[0964] Step A: 2-({4'-[(Benzofuran-2-carbonyl)-amino]-biphenyl-4-carbonyl}-amino)-pentanedioic acid di-tert-butyl ester

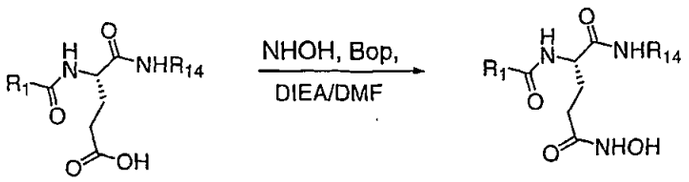
BOP coupling of 2-[(4'-Amino-biphenyl-4-carbonyl)-amino]-pentanedioic acid di-tert-butyl ester (349 mg, 0.77 mmol) with 2-Benzofuran carboxylic acid (124 mg, 0.77 mmol, 1 equiv.) was carried out according to procedures in step A of Example 6B to give 185 mg of 2-({4'-[(Benzofuran-2-carbonyl)-amino]-biphenyl-4-carbonyl}-amino)-pentanedioic acid di-tert-butyl ester in 40% yield. MS (ESI) *m/z* 597.

[0965] Step B: N-({4'-[(1-benzofuran-2-ylcarbonyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-glutamic acid

Hydrolysis of 2-({4'-[(Benzofuran-2-carbonyl)-amino]-biphenyl-4-carbonyl}-amino)-pentanedioic acid di-tert-butyl ester (185 mg, 0.31 mmol) was carried out according to procedures in step B of Example 6B to give N-({4'-[(1-benzofuran-2-ylcarbonyl)amino]-

1,1'-biphenyl-4-yl}carbonyl)-L-glutamic acid in 82.5 % yield (124 mg). MS (ESI) *m/z* 485.

Scheme 16



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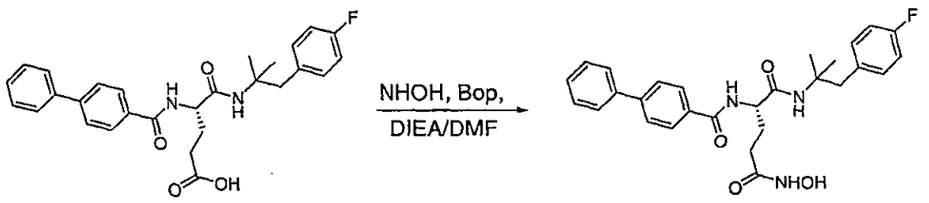
Example 32: N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^5-hydroxy-L-glutamamide



[0966] To a solution of the starting carboxylic acid (0.476 g, 1 mmol) in DMF (4 mL) under nitrogen is added BOP reagent (0.442 g, 1 mmol), followed by addition of hydroxylamine hydrochloride (0.076 g, 1.1 mmol), and DIEA (0.38 mL, 2.2 mmol). The reaction mixture was stirred for 24 hrs at room temperature. The mixture was then added slowly to 50 mL of water. The resulting white solid was collected, washed several times with water and dried under vacuum to give 350 mg of N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^5-hydroxy-L-glutamamide.

Example 33:

[0967] The following compounds were prepared according to procedures similar to those described in Example 32.

Example 33A: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^5-hydroxy-N^1-(3,4,5-trimethoxybenzyl)-L-glutamamide

[0968] MS (ESI) m/z 522.2; HRMS: calcd for $C_{28}H_{31}N_3O_7$ + H+, 522.22348; found (ESI_FTMS, $[M+H]^{1+}$), 522.22365.

Example 33B: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethylbenzyl)-N^5-hydroxy-L-glutamamide

[0969] MS (ESI) m/z 460.2; MS (ESI) m/z 919.4; HRMS: calcd for $C_{27}H_{29}N_3O_4$ + H+, 460.22308; found (ESI_FTMS, $[M+H]^{1+}$), 460.22328.

Example 33C: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^5-hydroxy-N^1-[2-(3-methoxyphenyl)ethyl]-L-glutamamide

[0970] MS (ESI) m/z 476.2; MS (ESI) m/z 951.4; HRMS: calcd for $C_{27}H_{29}N_3O_5$ + H+, 476.21800; found (ESI_FTMS, $[M+H]^{1+}$), 476.21792.

Example 33D: N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^5-hydroxy-N^1-[3-(trifluoromethoxy)benzyl]-L-glutamamide

[0971] MS (ESI) m/z 516.2; MS (ESI) m/z 1031.4; HRMS: calcd for $C_{26}H_{24}F_3N_3O_5$ + H+, 516.17408; found (ESI_FTMS, $[M+H]^{1+}$), 516.17389.

Example 34: *In vitro* fluorescence screen for Aggrecanase-1 inhibitors

Materials and Methods

[0972] This assay is a preliminary screen of potential aggrecanase-1 inhibitors at 11 concentrations to determine their ability to inhibit cleavage of a fluorescent peptide (Abz-TEGEARGSVI-Dap(Dnp)-KK). A GeminiXS fluorimeter (Molecular Devices) was turned on and the temperature was set to 30 °C, ~ 30 min before setting up the assay. The following buffers were used: 50 mM HEPES, pH 7.5; 100 mM NaCl; 5 mM $CaCl_2$; 0.1 % CHAPS; and 5% glycerol. The source of enzyme in the assay was purified recombinant human Aggrecanase-1 (rAgg1), used at 5 μg/ml (final concentration in the assay). The substrate used in the assay was the peptide (AnaSpec, MWT= 1645.8, stored at 4° C). A stock solution of peptide was prepared at 2 mg/ml in 100 % DMSO. The absorbance at 354 nm (ε=18172 $M^{-1}cm^{-1}$) was measured to determine the exact concentration of the stock solution. The stock solution was then diluted to 62.5 μM in buffer. The unused 100 % DMSO stock was stored at –80° C. The final concentration of

the substrate in the assay was 25 μM. Inhibitor solutions were prepared in 100 % DMSO with a 10X starting concentration, and serial dilutions were performed (in duplicate) across the dilution plate in 100 % DMSO.

[0973] The assay was performed as follows: 96-well plates were set up so that the final column of wells was used for controls. The total reaction volume of each well was 100 μl. Each compound was assayed in duplicate. Buffer was added to the entire 96-well plate (30 μl/well). rAgg1 was diluted to 25 μg/ml buffer just prior to addition on the plate, and added to the wells at 20 μl/well. 10 μl/ well of 10x inhibitors was added to the appropriate wells from the working plate, except for the control wells, to which are added 10 μl/ well of a 10X reference control compound or 100% DMSO. The mixtures were incubated for 10-15 min at 30° C. 40 μl/well of 62.5 μM peptide substrate was then added to the appropriate wells.

Results

[0974] The reaction was monitored for 30-40 min at 30°C., with λex = 340 nm and λ em = 420nm. The fluorescence was linear during this time and the slope of the line (Vmax/sec) represents the initial reaction rate,ν. The maximal rate of cleavage of substrate was determined in the absence of inhibitor. The percent inhibition of activity in the presence of inhibitor was calculated as follows: % inhibition = (1- ν (Rate, RFU/sec)/Maximal Rate(RFU/sec))*100. The IC_{50} was obtained by fitting the initial rate, ν, or % inhibition at each concentration of inhibitor to the following equation: y = (a-d)/($^{1+}$ C/ IC_{50})^n)+d. The assay results are shown in Tables 1, 2, and 3 below.

[0975] This model describes a sigmoidal curve with an adjustable baseline, a. y is the % inhibition or initial rate of reaction, C is the concentration of inhibitor under test. A is the limiting response as C approaches zero. As C increases without bound, y tends toward its lower limit, d. y is halfway between the lower and upper asymptotes when C= IC_{50}. n is the Hill coefficient. The sign of n is positive when the response increases with increasing dose and is negative when the response decreases with increasing dose (inhibition). (See, Knight, C.G. *Methods Enzymol.* 1995, 248, 18-34; Knight, C.G. et al., *FEBS Lett.* 1992, 296, 263-266; Jin, G. et al., *Anal. Biochem.* 2002, 302, 269-275).

Example 35: *In vitro* fluorescence screen for Aggrecanase-2 inhibitors

Materials and Methods

[0976] A continuous assay was used in which the substrate is a synthetic peptide containing a fluorescent group that is quenched by energy transfer. Cleavage of the peptide by the enzyme results in a large increase in fluorescence. The initial rates of this reaction were compared to the initial rates of reactions containing inhibitors in order to assess the potency of small molecules. The source of enzyme in the assay was purified recombinant human Aggrecanase-2 prepared at Wyeth Research (Biological Chemistry, Cambridge). More specifically, the form used is denoted as Ag2t-Phe_{628}-Strep (MW = 41,737). This form is truncated relative to the full-length enzyme and contains an affinity tag. Aliquots of this enzyme were stored at 80°C in 25mM Tris (pH 8.0), 100mM NaCl, 5mM $CaCl_2$, 10μM $ZnCl_2$, 10% glycerol. The substrate in the assay was a synthetic peptide that is designed after a portion of brevican, one of the naturally occurring substrates of Aggrecanase-2. This peptide contains the fluorescent group 2-aminobenzoyl (Abz) that is quenched by energy transfer to a 2,4-dinitrophenyl group (Dnp). The peptide (mass = 1740) is >95% pure based on HPLC analysis and has the sequence: Abz TESESRGAIY-Dap(Dnp)-KK-NH_2. Stock solutions of the substrate were prepared with MilliQ water and aliquots were stored at 80°C. The concentration of this substrate stock was spectrophotometrically determined using the extinction coefficient at 354nm of 18,172 M^{-1} cm^{-1}. The V_{max} and K_m for this enzyme/substrate reaction were determined to be insensitive to DMSO up to at least 10% (*v/v*). The assay buffer (pH 7.4) consisted of 50mM Hepes, 100mM NaCl, 5mM $CaCl_2$, 0.1% CHAPS, 5% glycerol.

[0977] Each well of the 96-well or 384-well plates contained a reaction consisting of assay buffer, purified Agg-2 (diluted with assay buffer), and varied concentrations of inhibitor (prepared by serial dilution in DMSO in 96-well polypropylene plates). The plates were then incubated at room temperature for 10 minutes. The enzymatic reactions were initiated by adding substrate to a final concentration of 25μM and mixed by pipetting up and down. The initial rates of the cleavage reactions were determined at room temperature with a fluorescence plate reader immediately after substrate addition. The Agg-2 assays were run on a Tecan Safire with the following wavelength settings: excitation – 316nm, 12nm bandwidth; emission – 432nm, 12nm bandwidth.

Results

[0978] A plot of time *vs.* RFU, representing the progress curve of the reaction, was generated. The slope for the portion of the progress curve that is most linear was determined. This slope (RFU/min) is the initial rate of the reaction. Plots of the inhibitor concentration *vs.* the initial cleavage rate were fit to the following equation: $y = Vmax*(1-(x^n / (K^n + x^n)))$, whereby x = inhibitor concentration, y = initial rate, V_{max} = initial rate in the absence of inhibitor, n = slope factor, and K = IC_{50} for the inhibition curve. The assay results are shown in Tables 1, 2, and 3 below.

Example 36: *In vitro* fluorescence assay of MMP-13 activity

Materials and Methods

[0979] A continuous assay was used in which the substrate is a synthetic peptide containing a fluorescent group (7-methoxycoumarin; Mca), which is quenched by energy transfer to a 2,4-dinitrophenyl group. When the peptide was cleaved by MMP, a large increase in fluorescence was observed. The source of enzyme in the assay was the recombinant human catalytic domain of MMP-13 (165 amino acids, residues 104-268, 19kDa) prepared at Wyeth-Research in Cambridge. The substrate used was the peptide Mca-PQGL-(3-[2,4-dinitrophenyl]-L-2,3-diaminopropionyl)-AR-OH. The assay buffer consisted of 50mM Hepes (pH 7.4), 100mM NaCl, 5mM $CaCl_2$, and 0.005% Brij-35. Each well of the 96-well plates contained a 200μL reaction mixture consisting of assay buffer, purified MMP (final concentration of 0.5nM, prepared by diluting with the assay buffer), and varied concentrations of inhibitor (prepared by serially diluting a given inhibitor in DMSO in 96-well polypropylene plate). The plates were then incubated at 30°C for 15 minutes. The enzymatic reactions were initiated by adding the substrate to a final concentration of 20μM, and mixing 10 times with a pipette. The final DMSO concentration in the assay was 6.0%. The initial rate of the cleavage reaction was determined at 30°C temperature with a fluorescence plate reader (excitation filter of 330nm and emission filter of 395nm) immediately after substrate addition.

Results

[0980] Plots of the inhibitor concentration *vs.* the percent inhibition were fit to the following equation: $y = (a-d)/[^{1+}(x/c)^b]+d$, a general sigmoidal curve with Hill slope, a to

d. x is the inhibitor concentration under test. y is the percent inhibition. a is the limiting response as x approaches zero. As x increases without bound, y tends toward its limit d. c is the inflection point (IC_{50}) for the curve. That is, y is halfway between the lower and upper asymptotes when x=c. b is the slope factor or Hill coefficient. (See, Knight, C.G. et al., *FEBS Lett.* 1992, 296, 263-266). The assay results are shown in Tables 1, 2, and 3 below.

Example 37: *In vitro* fluorescence assay of MMP-14 activity

Materials and Materials

[0981] A continuous assay was used in which the substrate is a synthetic peptide containing a fluorescent group (7-methoxycoumarin; Mca), which is quenched by energy transfer to a 2,4-dinitrophenyl group. When the peptide was cleaved by MMP, a large increase in fluorescence was observed. The source of enzyme in the assay was the recombinant human catalytic domain of MMP-14 (177 amino acids corresponding to Tyr89-Gly265 of mature human enzyme; 20 kDa; Chemicon International, Inc. (catalog number CC1041)). The substrate used was the peptide Mca-PQGL-(3-[2,4-dinitrophenyl]-L-2,3-diaminopropionyl)-AR-OH. The assay buffer consisted of 50mM Hepes (pH 7.4), 100mM NaCl, 5mM $CaCl_2$, and 0.005% Brij-35. Each well of the 96-well plates contained a 200μL reaction mixture consisting of assay buffer, MMP (final concentration of 25ng/ml, prepared by diluting with the assay buffer), and varied concentrations of inhibitor (prepared by serially diluting a given inhibitor in DMSO in 96-well polypropylene plate). The plates were then incubated at 30°C for 15 minutes. The enzymatic reactions were initiated by adding the substrate to a final concentration of 20μM, and mixing 10 times with a pipette. The final DMSO concentration in the assay was 6.0%. The initial rate of the cleavage reaction was determined at 30°C temperature with a fluorescence plate reader (excitation filter of 330nm and emission filter of 395nm) immediately after substrate addition.

Results

[0982] Plots of the inhibitor concentration *vs.* the percent inhibition were fit to the following equation: $y = (a-d)/[^{1+}(x/c)^b]+d$, a general sigmoidal curve with Hill slope, a to d. x is the inhibitor concentration under test. y is the percent inhibition. a is the limiting

response as x approaches zero. As x increases without bound, y tends toward its limit d. c is the inflection point (IC_{50}) for the curve. That is, y is halfway between the lower and upper asymptotes when x=c. b is the slope factor or Hill coefficient. (See, Knight, C.G. et al., *FEBS Lett.* 1992, 296, 263-266). The assay results are shown in Tables 1, 2, and 3 below.

Example 38: *In vitro* fluorescence assay of MMP-2 activity

Materials and Methods

[0983] A continuous assay was used in which the substrate is a synthetic peptide containing a fluorescent group (7-methoxycoumarin; Mca), which is quenched by energy transfer to a 2,4-dinitrophenyl group. When the peptide was cleaved by MMP, a large increase in fluorescence was observed. The source of enzyme in the assay was the recombinant human MMP-2 (66 kDa; Oncogene Research Products (catalog number PF023 from Calbiochem)). The substrate used was the peptide Mca-PQGL-(3-[2,4-dinitrophenyl]-L-2,3-diaminopropionyl)-AR-OH. The assay buffer consisted of 50mM Hepes (pH 7.4), 100mM NaCl, 5mM $CaCl_2$, and 0.005% Brij-35. Each well of the 96-well plates contained a 200μL reaction mixture consisting of assay buffer, MMP (final concentration of 25ng/ml, prepared by diluting with the assay buffer), and varied concentrations of inhibitor (prepared by serially diluting a given inhibitor in DMSO in 96-well polypropylene plate). The plates were then incubated at 30°C for 15 minutes. The enzymatic reactions were initiated by adding the substrate to a final concentration of 20μM, and mixing 10 times with a pipette. The final DMSO concentration in the assay was 6.0%. The initial rate of the cleavage reaction was determined at 30°C temperature with a fluorescence plate reader (excitation filter of 330nm and emission filter of 395nm) immediately after substrate addition.

Results

[0984] Plots of the inhibitor concentration *vs.* the percent inhibition were fit to the following equation: $y = (a-d)/[^{1+}(x/c)^b]+d$, a general sigmoidal curve with Hill slope, a to d. x is the inhibitor concentration under test. y is the percent inhibition. a is the limiting response as x approaches zero. As x increases without bound, y tends toward its limit d. c is the inflection point (IC_{50}) for the curve. That is, y is halfway between the lower and

upper asymptotes when x=c. b is the slope factor or Hill coefficient. (See, Knight, C.G. et al., *FEBS Lett.* 1992, 296, 263-266). The assay results are shown in Tables 1, 2, and 3 below.

Example 39: *In vitro* articular cartilage model for the inhibition of degradation of proteoglycan by small molecule compounds: Bovine articular cartilage explant cultures

[0985] This *in vitro* procedure was used to evaluate the effect and relative potencies of small molecule compounds to inhibit the degradation of proteoglycan in articular cartilage treated with Interleukin 1 alpha (IL-1α). Treatment of articular cartilage with IL 1α induces expression of a cascade of enzymes that initiates cartilage matrix degradation. This assay was utilized to select small molecule compounds that inhibit the enzyme activity and protects cartilage matrix degradation.

Materials and Methods

[0986] Articular cartilage: bovine metacarpal joints were disinfected with 10% Wescodyne followed by 70% ethanol. 6mm articular cartilage discs were prepared and rinsed once in PBS and medium, respectively. The discs were cultured in a stirring flask with serum-free medium for 5 days for equilibrium with one medium change. Small molecule compounds: stock solutions of test small molecule compounds (usually at 5mg/ml) were prepared in DMSO. Working solutions were diluted with DMSO and generally ranged from 0.1μg/ml to 10ug/ml. The DMSO stocks were stored at 20°C. Articular cartilage explant culture medium: DMEM, 2mM glutamax, 100 U/ml of antibiotic and antimycotic, 50 μg/ml ascorbate and 10mM Hepes (pH-7.0). Proteoglycan content-Dimethyl methylene blue (DMMB) solution: 1L-16mg DMMB, 10ml 100% ethanol, 29.5ml of 1M NaOH, 3.5 ml of 98% formic acid and water to 1L. Chondroitin sulphate sodium salt: 1.56-200 ug/ml serial dilutions.

[0987] For the explant culture, cartilage discs were cultured in serum-free medium for 48h or more. Discs were weighed and transferred to a 96-well plate, 1 disc per-well. 0.2ml of medium containing 5ng/ml of IL-1 and different concentrations of compounds were added to each well, with 3 wells allocated for each treatment. The medium was collected at days 1, 2, & 3 and replaced accordingly.

[0988] For the DMMB assay, conditioned medium (CM) samples were diluted with medium. 10ul of each standard or diluted sample was added in duplicate into a 96-well-plate and 200µl of DMMB solution was added into each well. Absorbance at 520nm was measured for each well. Proteoglycan contents in CM were calculated daily.

Results

[0989] The proteoglycan contents are expressed as ug per mg of cartilage. The inhibitory effect of the compounds is expressed as percentage. (See, Tortorella, M.D. et al., *Science* 1999, 284, 1664-1666). The assay results are shown in Tables 1, 2, and 3 below.

TABLE 1

Example	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1	bovine	bovine
8SSSS	>200,000								
7	150		1,800	~ 13,000	3,000	~13,000	>100,000	61	28
8C	110		1,200	~50,000	6,000	~25,000	>100,000	68	34
8B	460		1,900	~50,000	5,600	~25,000	>100,000	54	22
8A	150		900	~40,000	4,400	~25,000	>100,000	75	29
11	110		~ 800	~ 5,000	~ 1,000	~ 2,000	~ 2,000	78	52
12A	700		~ 5,000	~ 6,000	~ 2,000	~ 2,000	~ 2,000	41	18
12B	35000								
8D	220		2,800	~25,000	4,400	17,000	>100,000	67	27
8E	90		746	~25,000	3,700	~25,000	> 200,000	79	34
8NNNNNN	~40,000								
13B	~50,000								
8F	30	12	304	~22,000	5,630	~25,000	> 200,000	81	56
17VV	7900								
13A	1500		~67,000	>100,000	~67,000	> 100,000	>100,000	37	18
13C	9600								
13D	750		~26,000	>200,000	>200,000	>100,000	>100,000	51	25
13E	~ 25,000								
13F	~ 200								
8G	80		614	~50,000	~50,000	~25,000	>100,000	76	39
8OOOOOO	670								
8H	200		266	~50,000	3,310	~25,000	>100,000	85	67
8I	500								
12E	1800								
12C	25000								
12D	> 100,000								
8K	300								

Example	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1	bovine	bovine
8L	55		189	~50,000	10,500	21,500	> 100,000	87	79
8J	360								
8M	120		856	~50,000	8,000	13,000	> 100,000	85	17
8N	290								
8O	75	82	1,300	31,400	5,000	~ 22,000	no inh	69	34
8P	290								
8Q	11	31	400	37,300	6,100	~ 22,000	no inh	66	24
8R	16	5	50	42,400	10,400	~ 22,000	no inh	86	78
8S	150	245	1,300	> 200,000	3,130	~25,000	no inh	51	40
8T	300							51	20
8U	200							63	26
8V	160		1,100	~ 67,000	3,430	~ 30,000	> 100,000	73	45
8W	75		971	~ 22,000	~ 2,500	~25,000	no inh		
8X	100		1,100	~ 67,000	7,000	~ 25,000	no inh		
8Y	50		520	~ 67,000	5,534	~ 25,000	no inh		
8Z	80		680	~ 67,000	3,820	~ 25,000	no inh		
8BB	74		650	19,000	2,300	~ 25,000	no inh		
8AA	370								
33D	< 10		13.4	52	3.3	73.6	~ 1,560		
33C	< 10		25	29	4.5	110	1,500		
Control (33A)	<10		2.6	32	4.7	112	1,750		
8CC	22	19	121	~ 22,000	5,655	~ 25,000	no inh	94	71
13G	~2500								
8DD	94		930	~ 22,000	4,580	16,200	no inh	89	50
14	60% @ 16,700								
15A	> 22,000								
15B	67 % @ 7,500								
15C	50 % @ 7,500								
15D	86% @ 7,500								
15E	3500								
33B	< 30								
8PPPPPP	>33,000								
23	> 6000								
24A	1100								
24B	~2200								
24C	~300								
20	~ 22,000								
21A	2500-7500								
21B	~ 6700								

Example	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1	bovine	bovine
21C	no inh								
21D	no inh								
22C	> 50,000								
8FFF	200		1000						
8GGG, step D	100							57	12
8AAAA	100								
8DDDD	110								
8HHHH	200								
8XX	300								
8FF	26	28						86	50
17WW	no inh								
17XX	no inh								
17YY	2000								
17ZZ	200								
17AAA	no inh								
8YY	530		4500						
8ZZ	210								
8AAA	48	44						83	55
8EE	200								
15F	600								
15G	2200								
15H	200								
6A	150		740	>50,000	29800	> 200,000	> 50,000		
8HH	160								
8II	44	39						75	40
8QQQQQQ	690								
17BBB	900								
8III	120								
8NNN	100	219	1750	14,000	> 10,000	>50,000	> 50,000	60	0
8JJJ	54	54	300	30,000	>20,000	>200,000	>200,000	74	26
8JJ	45	33	1100	17,000	27,000	>200,000	>200,000	70	17
10M	43	54	1100	~20,000	>20,000	>200,000	>50,000	67	35
10N	19	28	970	>50,000	7600	>200,000	>200,000	65	24
8OO	<30	6	44	>50,000	>20,000	>200,000	>200,000	87	40
22A	1000								
22B	200								
8KK	180								
8LL	55		990	24,000	50,000	200,000	200,000	40	0
10R	77	187	1900	>20,000	>20,000	>200,000	>50,000	41	0
8BBB	32	130	700	>50,000		no inh	> 200,000	35	0
8CCC	100							74	26
8ZZZ	100		1600	no inh	13,000	> 200,000	>50,000	72	34
8KKK	120		2000						

Example	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1	bovine	bovine
10C	240		>5000						
10E	370								
10F	130		>30000						
10D	480		3200						
10G	1000		4400						
8BBBB	100							40	0
8OOO	280		1000						
8LLL	230								
8PPP	130								
8QQQ	330								
8EEE	7900								
8MM	58	126	980						
9	200								
10A	840		2100						
10J	260								
10K	380		>100000						
10L	130		2000						
10B	150								
8MMM	40		500						
8RRR	82		680						
10H	300								
8SSS	64		470	>50,000	10300				
10O	470								
8UUU	61	60	660	~50,000	8900	>200,000	no inh		
10P	700								
10Q	98		3000	~50,000		>50,000	no inh		
8PP	<30	10	85	~50,000	6000	>66,600	> 200,000		
8NN	<30	14	133	~50,000	9000	no inh	>200,000		
8VVV	30	38	420	~50,000	5600	>66,600	no inh		
8TTT	>10000								
6C	150								
8DDD	300								
6B	300								
8SS	100		800	~50,000	12400	>66,600	no inh		
8TT	300								
8UU	200								
8WW	70		350	~50,000	13300	> 66,600	no inh		
8VV	100		1900	~50,000	9100	> 66,600	no inh		
8XXX	30		930	~50,000	7900	> 200,000	no inh		
8WWW	36		840	~200,000	7400	> 200,000	no inh		
8YYY	100		1600	> 50,000	9400	> 200,000	no inh		
8GGGG	30		160	>50,000	18600	no inh	no inh		

Example	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1	bovine	bovine
8FFFF	3600								
10I	320								
8RRRRRR	3600								
8KKKK	<30	4							
8LLLL	no inh								
8MMMM	47	57							
8IIII	<30	9							
8JJJJ	>50000								
8NNNN	3400								
8OOOO	52	60							
8PPPP	>50000								
8QQQQ	9600								
8RRRR	122								
8SSSSSS	146								
8TTTTTT	17300								
1	900								
2	111								
3	12700								
4	1100								
5	1800								
8EEEE, step D	400								
8UUUUUU	4000								
26	5000								
27	400								
28	400								
29	3000								
30	500								
31	1000								
6D	45								
6E	56								
8VVVVVV	46								

Table 2

Example	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1
8TTTT	> 17,000		> 22,000				
8UUUU	> 17,000		~ 67,000				
8VVVV	> 17000		> 67,000				
8WWWW	8300		> 67,000				
8XXXX	> 50,000		>200,000				
8YYYY	1500		>200,000				
8ZZZZ	> 17000		> 22,000				
8AAAAA	372		410				
8BBBBB	> 17000		20900				
8CCCCC	107		11000				
8DDDDD	315		1100				
8EEEEE	> 50000		>200,000				
8FFFFF	92		710	>100,000			
8GGGGG	> 50,000						
8HHHHH	357						
8IIIII	813		1900				
8JJJJJ	191		1100				
8KKKKK	> 50,000		> 22,000				
8LLLLL	> 17,000		>200,000				
8MMMMM	20000		~ 22,000				
8NNNNN	1200		1,893 +/- 76				
8OOOOO	> 50,000		> 200,000				
8PPPPP	157		2967				
8QQQQQ	108		1165				
8RRRRR	129		2905				
8SSSSS	208		2470				
8TTTTT	389		2011				
8UUUUU	317		2119				
8VVVVV	221		1558				
8WWWWW	> 17,000		> 67,000				
8XXXXX	246		1450				
8YYYYY	87		2800	~ 20,000			
8ZZZZZ	<30		63	>100,000			
16	< 30 nM		467				
17A	116		1123				
17B	204		1020				
18D	4400		> 22,000				
17C	< 30 nM		80				
17D	> 17,000		>				

Example	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1
	nM		200,000				
17E	251		1040				
12F	~ 3,000 nM		3,000 - 8,000				
17F	1700		~ 8,300				
17G	1600		3,000 - 8,000				
17H	1000		~ 22,000				
8AAAAAA	534		1759	-			
17I	< 30		217 +/- 8	~100,000			
17J	~5,600		~ 30,000	-			
17K	1200		~ 3,700	-			
17L	133		226	-			
18E	2200		> 11,000	-			
17M	~ 310		> 11,000	-			
17N	40		42	11,200 +/- 1,200			
8MMMMMM	550		5100	-			
8BBBBBB	470		2671	-			
18F	> 67,000		> 67,000	-			
17O	8500		~ 22,000	-			
17P	126		58	-			
17Q	~ 13,000		> 30,000	-			
17R	73		142	6,000 +/- 400			
18	49		50	~ 1,600 nM			
19A	930		1020				
19B	3200		590				
8CCCCCC	2400		> 22000				
17S	4600		10100				
17T	3200		7200				
17U	1800		~ 6700				
19C	140 +/- 20		75				
17V	90		1800				
17W	> 25,000		~ 67000				
17X	2000		~ 22000				
8DDDDDD	2400		> 22000				
17Y	<30		156				
19D	210		223				
19E	49		1120				
17Z	170		3140				
17AA	3500		5700				

Example	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1
17BB	3600		2900				
17CC	2900		2970				
17DD	<30nM		1190				
17EE	<30nM		194				
17FF	690		13900				
17GG	34		113				
17HH	2200		6320				
17II	~ 1000-3000		~ 10,000				
17JJ	2400		19454				
15I	430		1593				
15J	510		~ 3,125				
12G	> 25000		11700				
12H	1200		1635				
12I	> 25000		> 20,000				
17KK	> 25000		> 67,000				
19F	68		163				
17LL	87		1193				
17MM	46		2707				
19G	270		146				
19H	69		158				
18G	~ 8300						
17NN	200		729				
8EEEEEE	5000						
17OO	<30		1677				
8FFFFFF	3900		18131				
8GGGGGG	4200						
8HHHHHH	38		46				
8IIIIII	2900		11908				
8JJJJJJ	300		943				
8KKKKKK	350		1674				
17QQ	> 25,000		~22000				
12J	~ 8,000		~22000				
12K	~ 25,000		>22000				
12L	~ 22,000		>22000				
17RR	<30		26				
17SS	450		3959				
17TT	120		173				
8LLLLLL	>25000		>100000				
15Y	220		841				
15Z	1400		6036				
15AA	44		327				
15BB	53		527				
17UU	<30		39				

Table 3

Example	Agg1 IC_{50} (nM)	K_i Agg1 (nM)	Agg 2 IC_{50} (nM)	K_i Agg2 (nM)	MMP -13	MMP-2	MMP -14	MMP-8	MMP-12
8WWWWWW	<03	7.1	50	72		2600		1000	5800
8XXXXXX	<30	<3	20	60		7500		4100	1600
8YYYYYY	<30	13.5	30	160		4700		737	365
8ZZZZZZ	<30		120						
8AAAAAAA	80		550						
8BBBBBBB	110		1000						
8CCCCCCC	50		680						
8DDDDDDD	<30		220						
8EEEEEEE	37		510						
8FFFFFFF	200		4200						
8GGGGGGG	60		160						
8HHHHHHH	50		180						
8IIIIIII	<30		42						
8JJJJJJJ	<30		53						
8KKKKKKK	<30		<30						
8LLLLLLL	228		3380						
8MMMMMMM	198		614						
8NNNNNNN	<30	<3	<30	37		2150		1210	680
8OOOOOOO	<30		100-400						
8PPPPPPP	3116		48% 16700						
8QQQQQQQ	NT		NT						
8RRRRRRR	70-210		48% 1200						
8SSSSSSS	57	22	230	356					
8TTTTTTT	707		20% 11000						
8UUUUUUU	<30	<3	60	60		5180		2030	410
8VVVVVVV	<30	7	51% 140	305		570		410	770
8WWWWWWW	<30	<3	50	42		1080		370	630
8XXXXXXX	<30	4.5	20-70	56					
8YYYYYYY	<30	27	200-600	197					
8ZZZZZZZ	<30	12.7	200-600	290					
8AAAAAAAA	<30	86	600-1800	1147					
8BBBBBBBB	300		200-600						
8CCCCCCCC	140		5200						
8DDDDDDDD	50		1000						
8EEEEEEEE	<30	3.8	60-200	79					
8FFFFFFFF	<30		200						
8GGGGGGGG	40		3400						
8HHHHHHHH	60		3000						
8IIIIIIII	65% 200		90-270						
8JJJJJJJJ	<30		800-2500						
8KKKKKKKK	70		270-800						
8LLLLLLLL	<30	<3	60-200	156					
8MMMMMMMM	<30	<3	60-200	38					
8NNNNNNNN	<30	<3	70-200	151					
8OOOOOOOO	<30		200-600						

Example	Agg1 IC_{50} (nM)	K_i Agg1 (nM)	Agg 2 IC_{50} (nM)	K_i Agg2 (nM)	MMP -13	MMP-2	MMP -14	MMP-8	MMP-12
8PPPPPPPP	<30		200-600						
8QQQQQQQQ	<30		3300						
8RRRRRRRR	57% 70		7200						
8SSSSSSSS	<30	5.4	70-200	51					
8TTTTTTTT	20-70	37.6	100-300	359					
8UUUUUUUU	100		700						
8VVVVVVVV	60% 16700		50% 50000						
8WWWWWWWW	20-70	40.6	100-300	526					
8XXXXXXXX	100		1700						
8YYYYYYYY	<30	6.2	100-300	143					
8ZZZZZZZZ	20-70		9900						
8AAAAAAAAA	<30	6.7	98	45					
8BBBBBBBBB	<30	11.5	100-300	681					
8CCCCCCCCC	<30		900						
8DDDDDDDDD	2400		50% 7400						
8EEEEEEEEE	1200		50% 2500						
8FFFFFFFFF	270		62% 25000						
8GGGGGGGGG	30% 8300		28% 25000						
8HHHHHHHHH	<30		500						
8IIIIIIII	300-900		5% 2500						
8JJJJJJJJ	25% 25000		10% 25000						
8KKKKKKKKK	16% 25000		10% 25000						
8LLLLLLLL	<30		>300						
8MMMMMMMMM	<30	<3	30-100	87					
8NNNNNNNNN	<30	8.3	30-100	69					
8OOOOOOOOO	<30	2.7	~30	66		718		349	372
8PPPPPPPPP	<30	11.5	30-300	126		7240		2550	2890
8QQQQQQQQQ	>900		>8300						
8RRRRRRRRR	>8300		100000						
8SSSSSSSSS	<30	8.8	200	157					
8TTTTTTTTT	<30	6.7	59	54					
8UUUUUUUUU	<30	6.9	83	75					
8VVVVVVVVV	<30	4.5	77	81					
8WWWWWWWWW	>25000		>100000						
8XXXXXXXXX	<30	18.2	25	71.6		2610		1790	597
8YYYYYYYYY	<30	39.6	250	349		25500		13200	3710
8ZZZZZZZZZ	<30	4.7	30-90	123		8280		2440	2860
8AAAAAAAAAA	<30	28.9	100-300	204		6970		2230	2240
8BBBBBBBBBB	22000		>200000						
8CCCCCCCCCC	1040		7400						
8DDDDDDDDDD	<30	27.2	90	218		4000		763	628
8EEEEEEEEEE	<30	23.2	80	180		6400		2500	1070
8FFFFFFFFFF	>400		>2700						
8GGGGGGGGGG	<30	42	>300	723		1300		>5000	>10,000
8HHHHHHHHHH	<30	11.7	>100	405		8000		3400	>10,0

Example	Agg1 IC_{50} (nM)	K_i Agg1 (nM)	Agg 2 IC_{50} (nM)	K_i Agg2 (nM)	MMP -13	MMP-2	MMP -14	MMP-8	MMP-12
									00
8IIIIIIIII									
15O	52		3132						
15P	<30		255						
15K	<30		379						
15L	47		413						
15M	<30		789						
15N	91		103						
15U	53% 100		600						
15V	47% 40		700						
15Q	158		1939						
15R	560		48% 11000						
15S	30% 1850		41% 33000						
15U	53% 1000		30% 11000						
15W	56% 1900		59% 11000						
15X	46% 1900		52% 11000						

Example 40: Aggrecanase inhibitors in human osteoarthritic cartilage explant studies and effect on Aggrecan metabolism in human osteoarthritic cartilage

[0990] The loss of cartilage matrix in osteoarthritis (OA) is associated with increased loss of type II collagen by collagenases and aggrecan loss by aggrecanases. Depletion of aggrecan is one of the earliest changes observed in osteoarthritis (Lohmander, LS et al., *Arthritis & Rheum* 1993, 36,1214-1222). Aggrecan is a chondroitin sulfate and keratan sulfate-bearing proteoglycan. Aggrecanase 1 and Aggrecanase 2 cleave aggrecan within the interglobular domain at the aggrecanase site between residues Glu^{373} and Ala^{374} (Sandy, JD et al., *J Clin Invest.* 1992, 89, 1512–1516). Aggrecan cleavage by aggrecanase results in the release of a large sulfated glycosaminoglycan (sGAG)-containing aggrecan fragments which diffuse out of the cartilage matrix. Neoepitope antibodies have been generated to recognize these aggrecanase generated aggrecan fragments (Hughes, CE et al., *Biochem J.* 1995, 305, 799–804). Aggrecan fragments in inflammatory and OA synovial fluid have been reported as being generated by cleavage at the aggrecanase site (Malfait, A-M et al., *J*

Biol Chem. 2002, 277, 22201-22208). Inhibiting aggrecanase activity is an attractive therapeutic target for OA. In this example, we investigated the effects of a selective aggrecanase inhibitor on the fate of existing and newly synthesized aggrecan in human OA cartilage.

Materials and Methods

[0991] **Human OA Cartilage Explant Culture:** Discarded tissues from consented knee replacement patients were obtained from New England Baptist Hospital (Brookline, MA) in sterile phosphate buffered saline (PBS) after about 2-4 hrs post surgery. Cartilage slices were harvested from the knee specimens and washed several times in PBS. These cartilage slices were cut into appropriate pieces (6-8 mm) and rinsed in PBS and then in media and further cultured for additional days as cartilage explants. The medium consisted of Dulbecco's Modified Eagle's medium (DMEM, JRH Biosciences, Lenexa, KS), 50μg/ml ascorbic acid (Wako, Osaka, Japan), 10mM HEPES, pH 7.0 (Mediatech, Herndon, VA), 2mM L-glutamine (Mediatech), 100 U/ml antibiotic-antimycotic solution (Mediatech).

[0992] **Test compounds:** The test compounds are described in Examples 8OO, 8NNNNNNN, and 8WWWWWWW. Stock solutions of the compounds were prepared at 1mg/ml in DMSO, aliquoted and stored at -20°C. Working solutions of the compounds were made in DMSO and added to the culture for efficacy studies.

[0993] **Efficacy study:** Cartilage explants were cultured for 2-3 days in DMEM medium in a 37°C and 5% CO_2 environment to equilibrate the tissue. Explants were weighed (~250mg) and placed in wells of a 24-well culture dish in 1 ml of medium and 3 replicates per treatment group. For the efficacy study, cartilage explants were cultured for 6 days in the presence or absence of various concentrations of the test compound. The media was replaced on day 3 and the experiment was terminated on day 6. Total aggrecan content of conditioned media was measured by a colorimetric assay with DMMB (Farndale, RW et al., *Biochim Biophys Acta.* 1986, 883, 173-177).

[0994] **Cartilage aggrecan metabolism study:** Cartilage metabolism study was performed with test compound 8OO. Cartilage explants immediately after harvest were cultured in the presence or absence of test compound 8OO. On day 3, media was collected and replaced with media, test compound and labeled sulfate ($^{35}SO_4$, 5 mCi,

Perkin Elmer, Boston, MA). On day 6, media was collected, explants washed and replaced with media and test compound 8OO. On Day 9, media was collected, explants washed and the remaining tissue was digested with Proteinase K (Sigma). Samples were separated on NAP10 columns (Pharmacia, Uppsala, Sweden) to separate free label and newly synthesized labeled aggrecan. Labeled aggrecan molecules were counted using Opti-Fluor (Perkin Elmer) and a liquid scintillation-measuring instrument (Beckman Coulter, Fullerton, CA). The percentage of newly synthesized aggrecan in cartilage and media was estimated.

[0995] **Western analysis:** Aggrecan fragments in conditioned medium were analyzed by western analysis using neoepitope antibody, BC-3 designed to recognize the Aggrecanase-generated N-terminal interglobular neoepitope ^{374}ARGS. Equal cartilage weight equivalent conditioned media from each replicate well per treatment group was pooled and digested with Chondroitinase ABC (Sigma, St Louis, MO), Keratinase I (Seikagaku America, Falmouth, MA) and Keratinase II (Seikagaku America, Falmouth, MA) for 2 h at 37°C. Samples were concentrated by YM-10 centrifugal filter device (Millipore Corp., Bedford, MA), lyophilized and reconstituted with equal volume of water. Samples were separated under reducing conditions on 4-12% gradient Tris-glycine gels (Invitrogen, Carlsbad, CA). Proteins from the gels were transferred to nitrocellulose membranes. Immunoblots were probed using Mab BC-3 (Abcam, Cambridge, MA). Incubation with primary and alkaline-phosphatase-conjugated secondary goat anti-mouse IgG (Promega Corp., Madison, WI) was performed overnight at 4°C and at room temperature for 1 h, respectively. The immunoblots were incubated with NBT/BCIP substrate (Promega Corp., Madison, WI) at room temperature to achieve optimum color development. The aggrecan fragments containing the ARGS neoepitope were quantitated by densitometry analysis and the percentage inhibition of aggrecan degradation by test compounds was determined.

Results

[0996] **Efficacy of test compounds 8OO, 8NNNNNNN, and 8WWWWWWW:** Information on human donors including age and sex are shown in Table 4b, 5b, and 6b. Cartilage from all the donors when placed in culture exhibited Aggrecanase-mediated aggrecan cleavage and when treated with test compounds showed dose dependent

inhibition of Aggrecanase-mediated aggrecan cleavage. Results of the inhibition of aggrecanase activity in terms of inhibition of aggrecanase generated aggrecan fragments by test compounds are shown in Table 4a, 5a, and 6a. Based on these results, EC_{50} of test compound 8OO was determined to be about 150 ng/ml (Figure 1), EC_{50} for test compound 8WWWWWWW was around 40-160 ng/ml; and EC50 for test compound 8NNNNNNN was less than 40 ng/ml. However, test compound 8WWWWWWW and test compound 8NNNNNNN were tested in only 8 and 4 donors, respectively. Test compound 8OO was tested in a total of 15 donors.

[0997] **Effect of test compound 8OO on Aggrecan Metabolism**: Articular cartilage from 3 human OA donors was analyzed for the effect of test compound 8OO on newly synthesized aggrecan. Cartilage from all 3 donors showed the ability to synthesize new aggrecan molecules that was either in the cartilage matrix or released into conditioned medium. Cartilage from all 3 donors when treated with compound 8OO showed dose dependent increase in newly synthesized aggrecan content of the cartilage matrix and an equivalent decrease in aggrecan released into the medium (Figure 2).

[0998] Aggrecanase activity is a characteristic of human osteoarthritis throughout the disease process. Analysis of aggrecan released from human osteoarthritic articular cartilage revealed significant ongoing degradation of aggrecan by Aggrecanases in human donors tested. Inhibition of Aggrecanase activity by Aggrecanase selective inhibitors reduced release of aggrecan degradation products from the articular cartilage matrix.

[0999] Since newly synthesized aggrecan appeared to be susceptible to degradation by Aggrecanases, selective Aggrecanase inhibition resulted in a net increase in aggrecan incorporation into the cartilage matrix. These results indicate that inhibition of Aggrecanases will reduce aggrecan degradation in human osteoarthritic articular cartilage throughout the disease process, and also result in a net increase in extracellular matrix aggrecan.

Table 4

A) Efficacy of test compound 8OO in human explant studies

Compound 8OO (BC3 analysis)		
Conc. of compound (ug/ml)	Average of 15 donors	
	% inhibition	SDM
0.02	8.52	
0.04	26.16	*5.33*
0.08	42.93	*7.86*
0.15	49.03	*7.87*
0.3	56.40	*5.95*
0.6	73.92	*5.24*
1.25	83.36	*5.59*
2.5	100.94	*4.12*
5	98.88	*1.32*
10	101.60	*0.99*
~EC50 = 150 ng/ml		

B) Human donor information for test compound 8OO studies

Compound 8OO (Donor info)	
Sex	Age
F	65
M	83
M	70
F	56
F	76
M	53
F	77
F	74
F	75
M	79
M	61
F	57
M	72
M	70
M	62

Table 5

A) Efficacy of test compound 8WWWWWWW in human explant studies

Compound 8WWWWWWW (BC3 analysis)		
Conc. of compound (ug/ml)	Average of 8 donors	
	% inhibition	SDM
0.01	2.85	*2.85*
0.02	46.39	*15.95*
0.04	23.50	*10.57*
0.08	76.91	*5.99*
0.15	88.47	*3.25*
0.3	95.03	*1.70*
0.6	98.03	*0.90*
1.25	100.30	*0.55*
~EC50 = 40-160 ng/ml		

B) Human donor information for test compound 8WWWWWWW studies

Test compound (Donor info)	
Sex	Age
F	69
F	69
F	63
M	60
M	57
F	72
F	65
F	75

Table 6

A) Efficacy of test compound 8NNNNNNN in human explant studies

Test compound 8NNNNNNN (BC3 analysis)		
Conc. of compound (ug/ml)	Average of 4 donors	
	% inhibition	SDM
0.04	70.22	
0.08	84.46	
0.15	66.74	*10.97*
0.3	73.14	*19.73*
0.6	98.93	*0.92*
1.25	99.43	*1.44*
2.5	98.66	*2.20*
5	100.21	*1.15*
10	101.15	*0.42*
~EC50 = less than 40 ng/ml		

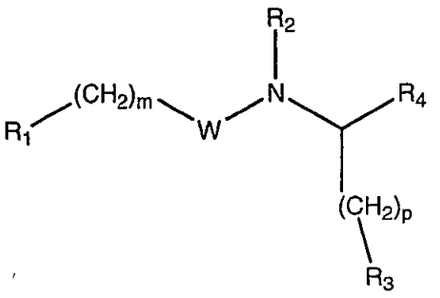
B) Human donor information for test compound 8NNNNNNN studies

Test compound (Donor info)	
Sex	Age
M	63
F	68
F	72
F	60

[1000] While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

What is claimed is:

1. A compound of the formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

W is –C(O)-, -OC(O)-, –NHC(O)-, -C(O)O-, or –C(O)NH-;

R_1 is phenyl, heteroaryl, biphenyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each optionally substituted with one or more of R_5 or R_6, and when R_1 is substituted with more than one of R_5 or R_6, the substituents can be identical or different;

R_2 is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -$(CH_2)_nR_{11}$, -OH, or -O-(C_1-C_6) alkyl;

R_3 is -CO_2H, -$CONH_2$, -CONHOH, -$CONHSO_2R_7$, tetrazole, -SO_2NHR_7, -SO_3H, -PO(OH)NH_2, -PO(OH)OR_7, -$CONHR_7$, -$COOR_7$, an acid mimetic group, or a 5 or 6-membered heterocycloalkyl or heteroaryl containing 1 to 4 heteroatoms selected from O, N, S;

R_4 is -CO_2H, -$CONH_2$, -$(CH_2)_nOR_7$, or -$CONR_9R_{10}$;

R_5 is aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, -CO-(C_1-C_6) alkyl, -CO-aryl, -CO-heteroaryl, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2NH-aryl, -SO_2NH-heteroaryl, -$NHSO_2$-(C_1-C_6) alkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl, -CONH-heteroaryl, (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-

C_6) cycloalkyl, or -CONH-(C_3-C_6) cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different;

R_6 and R_{12} are each independently hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6) alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_9 and R_{10} are each independently hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkyl-OH, (C_1-C_6) alkyl-O-(C_1-C_6) alkyl, aryl, cycloalkyl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_9 and R_{10} together may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_{11} is aryl, heteroaryl, or cycloalkyl;

R_{13} is halogen, -O-(C_1-C_6) alkyl, -CO_2H, -OH, -CF_3, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl

substituted with -OH, aryl substituted with $-NH_2$, aryl substituted with -O-(C_1-C_6) alkyl,

$-(CH_2)_n$-aryl, or $-(CH_2)_n$-heteroaryl;

m is 0-4;

n is 0-4; and

p is 0-2.

2. The compound or salt of claim 1, wherein W is -CO.

3. The compound or salt of claim 1 or claim 2, wherein R_3 is $-CO_2H$.

4. The compound or salt of any one of claims 1 to 3, wherein R_1 is bicyclic aryl optionally substituted with one or more of R_5 and R_6, wherein R_5 and R_6 are defined as in claim 1.

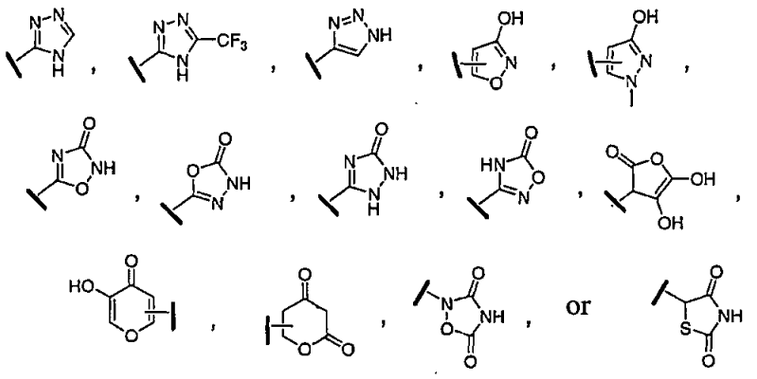
5. The compound or salt of any one of claims 1 to 3, wherein R_1 is tricyclic aryl optionally substituted with one or more of R_5 and R_6, wherein R_5 and R_6 are defined as in claim 1.

6. The compound or salt of any one of claims 1 to 3, wherein R_1 is biphenyl optionally substituted with one or more of R_5 and R_6, wherein R_5 and R_6 are defined as in claim 1.

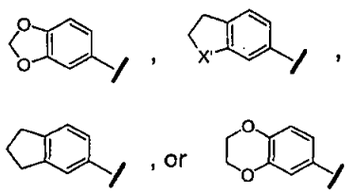
7. The compound or salt of any one of claims 1 to 6, wherein m is 0 and p is 2.

8. The compound or salt of any one of claims 1 to 7, wherein R_4 is $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, or $-CONR_9R_{10}$, wherein R_7, R_9, R_{10}, and n are defined as in claim 1.

9. The compound or salt of any one of claims 1 to 8, wherein R_3 is



10. The compound or salt of any one of claims 1 to 9, wherein R_5 is



and X' is O, S, or NH.

11. The compound or salt of claim 1, wherein

W is –CO,

R_2 is hydrogen,

R_3 is $-CO_2H$,

R_1 is biphenyl optionally substituted with one or more of R_5 and R_6,

R_4 is $-CONR_9R_{10}$,

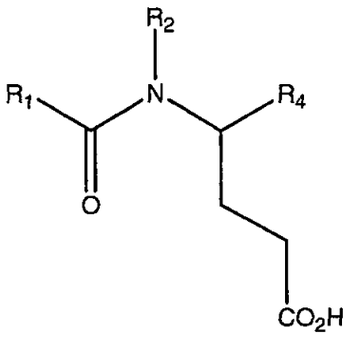
m is 0,

p is 2, and

R_5, R_6, R_9, and R_{10} are defined as in claim 1.

12. The compound or salt of any one of claims 1 to 11, wherein the compound or pharmaceutically acceptable salt of the compound is the S-enantiomer with respect to the carbon to which R_4 is bound.

13. The compound of claim 1 of the formula (Ia):



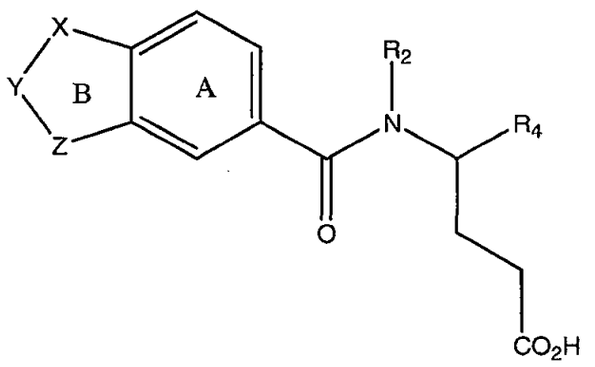
(Ia)

or a pharmaceutically acceptable salt thereof,

wherein

R_1, R_2, and R_4 are defined as in any one of claims 1, 3, 4, 5 or 8.

14. The compound of claim 1 of the formula (Ib):



(Ib)

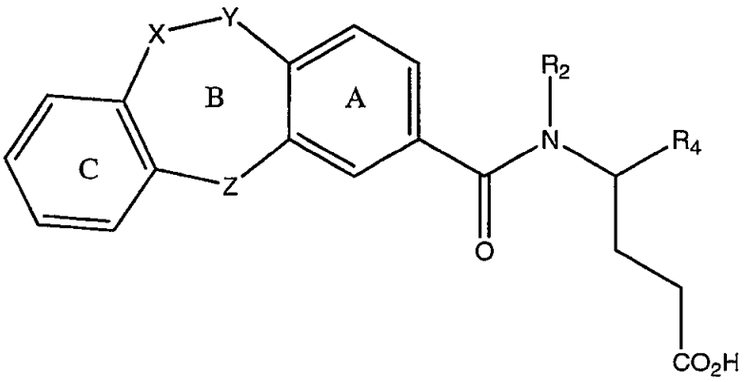
or a pharmaceutically acceptable salt thereof,

wherein

X, Y, and Z are each independently $(CH_2)_n$, O, S, NR_7, CO, or SO_2; or X, Y, and Z form a benzene in ring B; ring A and ring B are each independently optionally substituted with one or more of R_5 and R_6; and

R_2, R_4, R_5, R_6, R_7, and n are as defined in any one of claims 1, 8 or 10.

15. The compound of claim 1 of the formula (Ic):



(Ic)

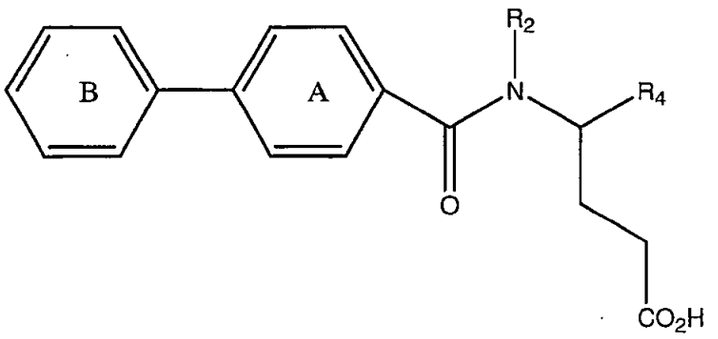
or a pharmaceutically acceptable salt thereof,

wherein

X, Y, and Z are each independently $(CH_2)_n$, O, S, NR_7, CO, or SO_2; or X, Y, and Z form a benzene in ring B; ring A, ring B, and ring C are each independently optionally substituted with one or more of R_5 and R_6; and

R_2, R_4, R_5, R_6, R_7, and n are as defined in any one claims 1, 8 or 10.

16. The compound of claim 1 of the formula (Id):



(Id)

or a pharmaceutically acceptable salt thereof,

wherein

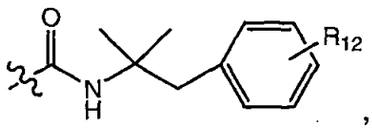
ring A and ring B are each independently optionally substituted with one or more of R_5 and R_6; and

R_2, R_4, R_5, and R_6 are as defined in any one of claims 1, 8 and 10.

17. The compound of claim 16 or a pharmaceutically acceptable salt thereof, wherein

R_2 is hydrogen,

R_4 is



, and

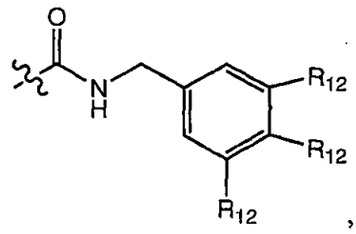
R_{12} is -F.

18. The compound of claim 15 or a pharmaceutically acceptable salt thereof, wherein

each of X, Y, and Z is independently $(CH_2)_n$, with n = 1 for one of X, Y, and Z and n = 0 for the other of X, Y, and Z;

R_2 is hydrogen;

R_4 is



, and

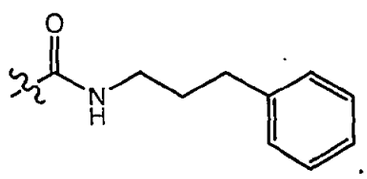
each R_{12} is $-OCH_3$.

19. The compound of claim 15 or a pharmaceutically acceptable salt thereof, wherein

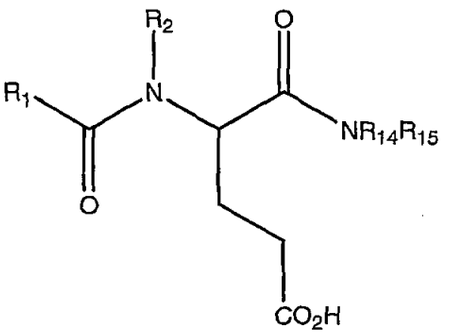
each of X, Y, and Z is independently $(CH_2)_n$, with n = 1 for one of X, Y, and Z, and n = 0 for the other of X, Y, and Z;

R_2 is hydrogen; and

R_4 is



20. A compound of the formula (II):



(II)

or a pharmaceutically acceptable salt thereof,

wherein

R_1 is phenyl, heteroaryl, biphenyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each optionally substituted with one or more of R_5 or R_6, and when R_1 is substituted with more than one of R_5 or R_6, the substituents can be identical or different;

R_2 is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -$(CH_2)_pR_{11}$, -OH, or -O-(C_1-C_6) alkyl;

R_5 is aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, -CO-(C_1-C_6) alkyl, -CO-aryl, -CO-heteroaryl, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2NH-aryl, -SO_2NH-heteroaryl, -$NHSO_2$-(C_1-C_6) alkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl, -CONH-heteroaryl, (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, or -CONH-(C_3-C_6) cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different;

R_6 and R_{12} are each independently hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2,

-OH, -SH, $-NR_7R_8$, $-CONR_7R_8$, $-NR_8COR_7$, $-NR_8CO_2R_7$, $-CO_2R_7$, $-COR_7$, $-SO_2-(C_1-C_6)$ alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl, $-SO_2R_7$, $-NR_7SO_2R_8$, $-SO_2NR_7R_8$; (C_1-C_6) alkyl, $-O-(C_1-C_6)$ alkyl, $-S-(C_1-C_6)$ alkyl, $-NH-(C_1-C_6)$ alkyl, $-NHCO-(C_1-C_6)$ alkyl, $-CONH-(C_1-C_6)$ alkyl, $-O-(C_3-C_6)$ cycloalkyl, $-S-(C_3-C_6)$ cycloalkyl, $-NH-(C_3-C_6)$ cycloalkyl, $-NHCO-(C_3-C_6)$ cycloalkyl, $-CONH-(C_3-C_6)$ cycloalkyl, heterocycloalkyl, $-(C_1-C_6)$ alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, $-O-(C_1-C_6)$ alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, $-O-(C_1-C_6)$ alkyl substituted with aryl, aryl, heteroaryl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, $-(CH_2)_n$-aryl, or $-(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_{11} is aryl, heteroaryl, or cycloalkyl;

R_{13} is halogen, $-O-(C_1-C_6)$ alkyl, $-CO_2H$, -OH, $-CF_3$, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl substituted with -OH, aryl substituted with $-NH_2$, aryl substituted with $-O-(C_1-C_6)$ alkyl, $-(CH_2)_n$-aryl, or $-(CH_2)_n$-heteroaryl;

R_{14} and R_{15} are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, heterocycloalkyl $-(CH_2)_n$-aryl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_{14} and R_{15} together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

n is 0-4, and

p is 0-2.

21. The compound or pharmaceutically acceptable salt of the compound of claim 1, wherein the compound is

N^2-(4-benzoylbenzoyl)-N^1-benzyl-L-α-glutamine,
N-(4-benzoylbenzoyl)-L-glutamic acid,
N^1-(1,3-benzodioxol-5-ylmethyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-butyl-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclopropyl-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclohexyl-L-α-glutamine,
N^1-benzyl-N^2-(4-thien-2-ylbenzoyl)-L-α-glutamine,
N^1-benzyl-N^2-[4-(2-furyl)benzoyl]-L-α-glutamine,
N^1-benzyl-N^2-[(4'-ethynyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-fluorobenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclooctyl-L-α-glutamine,
N^1-benzyl-N^2-(4-bromobenzoyl)-L-α-glutamine,
N^1-benzyl-N^2-[(2',5'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethoxybenzyl)-L-α-glutamine,
N^1-benzyl-N^2-(4-pyridin-4-ylbenzoyl)-L-α-glutamine,
N^1-benzyl-N^2-[(3',5'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^1-benzyl-N^2-[(4'-ethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^1-benzyl-N^2-[(3'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^1-benzyl-N^2-[(2'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^1-benzyl-N^2-[(2',6'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-cyclopentyl-L-α-glutamine,
N^1-[2-(acetylamino)ethyl]-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine,
N^1-2-adamantyl-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine,
N^1-(2-adamantylmethyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine,
N^1-benzyl-N^2-(4-pyridin-2-ylbenzoyl)-L-α-glutamine,
N^1-benzyl-N^2-(4-pyridin-3-ylbenzoyl)-L-α-glutamine,
N^1-benzyl-N^2-[4-(1,3-thiazol-2-yl)benzoyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methoxybenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3,4-dimethoxyphenyl)ethyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methoxyethyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(4-methoxyphenyl)ethyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(1-naphthylmethyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-methylbenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-furylmethyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-methoxybenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,4-dichlorobenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-(trifluoromethoxy)benzyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[3-(trifluoromethoxy)benzyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-(methylthio)benzyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-phenoxybenzyl)-L-α-glutamine,

N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3-methoxyphenyl)ethyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,4-dimethoxybenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methoxybenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dichlorobenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,5-difluorobenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^5-hydroxy-N^1-[3-(trifluoromethoxy)benzyl]-L-glutamamide,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^5-hydroxy-N^1-[2-(3-methoxyphenyl)ethyl]-L-glutamamide,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^5-hydroxy-N^1-(3,4,5-trimethoxybenzyl)-L-glutamamide,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,5-dimethoxybenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,5-dimethoxybenzyl)-N^5-hydroxy-L-glutamamide,
N^1-benzyl-N^2-[(4'-vinyl-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethylbenzyl)-L-α-glutamine,
N^1-benzyl-N^2-[(4'-ethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^1-benzyl-N^2-[(4'-propoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^1-benzyl-N^2-[(4'-butoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^1-benzyl-N^2-{[4'-(cyclobutylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine,
N^1-benzyl-N^2-{[4'-(cyclohexylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine,
N^2-{[4'-(allyloxy)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-dimethylbenzyl)-N^5-hydroxy-L-glutamamide,
N^2-(1,1'-biphenyl-4-ylacetyl)-N^1-(3-methoxybenzyl)-L-α-glutamine,
N^2-[(3-fluorophenyl)acetyl]-N^1-(3-methoxybenzyl)-L-α-glutamine,
N^2-{[4'-(acetylamino)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutamine,
N^1-benzyl-N^2-{[4'-(2-furoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine,
N^1-benzyl-N^2-({4'-[(4-fluorobenzoyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutamine,
N^2-{[4'-(benzoylamino)-1,1'-biphenyl-4-yl]carbonyl}-N^1-benzyl-L-α-glutamine,
N^1-benzyl-N^2-(5-phenyl-2-furoyl)-L-α-glutamine,
N^1-benzyl-N^2-[5-(3-ethoxyphenyl)-2-furoyl]-L-α-glutamine,
N^1-benzyl-N^2-[5-(3,5-dimethylphenyl)-2-furoyl]-L-α-glutamine,
N^1-benzyl-N^2-(2,2'-bifuran-5-ylcarbonyl)-L-α-glutamine,
N^1-benzyl-N^2-(5-thien-2-yl-2-furoyl)-L-α-glutamine,
N^2-[(2,2'-dimethyl-1,1'-biphenyl-4-yl)carbonyl]-N^1-(3-methoxybenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-phenylethyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[3-(trifluoromethyl)benzyl]-L-α-glutamine,
N^1-(4-aminobenzyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine,
N^1-(3-aminobenzyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(trifluoromethyl)benzyl]-L-α-glutamine,
N^1-benzyl-N^2-[(2-fluoro-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,

N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-fluorobenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine,
N^1-benzyl-N^2-(1,1'-biphenyl-3-ylcarbonyl)-L-α-glutamine,
N^1-benzyl-N^2-(3-thien-2-ylbenzoyl)-L-α-glutamine,
N^1-benzyl-N^2-[(3-chloro-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^1-benzyl-N^2-[(3-fluoro-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^1-benzyl-N^2-[(2,6-dimethoxy-1,1'-biphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(3-chlorophenyl)ethyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-fluorobenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3,4-difluorobenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2-methylbenzyl)-L-α-glutamine,
N^1-benzyl-N^2-({4'-[(3-methoxybenzyl)oxy]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutamine,
N^1-benzyl-N^2-({4'-[(3,5-dimethoxybenzyl)oxy]-1,1'-biphenyl-4-yl}carbonyl)-L-α-glutamine,
N^1-benzyl-N^2-{[4'-(2-naphthylmethoxy)-1,1'-biphenyl-4-yl]carbonyl}-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-2,3-dihydro-1*H*-inden-2-yl-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(2,3-dimethylbenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-phenylbutyl)-L-α-glutamine,
N^1-(2-benzylphenyl)-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methoxy-1,1'-biphenyl-3-yl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-methylbenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[4-fluoro-3-(trifluoromethyl)benzyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-heptyl-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-iodobenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-vinylbenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(3-thien-2-ylbenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^1-benzyl-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine,
N^1-(3-methoxybenzyl)-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-*tert*-butylbenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-iodobenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-vinylbenzyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(sec-butyl)-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(cyclopropylmethyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[4-(dimethylamino)benzyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-bromophenyl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-biphenyl-4-ylethyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2'-ethoxybiphenyl-4-yl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-ethynylbiphenyl-4-yl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4-(2-thienyl)phenyl]ethyl}-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-pyridin-2-ylphenyl)ethyl]-L-α-glutamine,

N^2-(biphenyl-4-ylcarbonyl)-N^1-[3-(dimethylamino)benzyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(3,3-diphenylpropyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(3,3-dimethylbutyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-isopropyl-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(pyridin-4-ylmethyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1,N^1-diethyl-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1-dimethylpropyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-4-yl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4'-(trifluoromethyl)biphenyl-4-yl]ethyl}-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-formylbiphenyl-3-yl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-{2-[4'-(trifluoromethyl)biphenyl-3-yl]ethyl}-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-methoxybiphenyl-3-yl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4'-methoxybiphenyl-4-yl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(3-bromophenyl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-pentyl-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-pyridin-4-ylphenyl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(*tert*-butyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-{[4'-(trifluoromethyl)biphenyl-3-yl]methyl}-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(2,2-dimethylpropyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[(4'-ethynylbiphenyl-3-yl)methyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(3-pyridin-2-ylbenzyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-hexyl-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(1-methyl-1-phenylethyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(1,1,3,3-tetramethylbutyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-morpholin-4-ylethyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(2-hydroxy-1,1-dimethylethyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-fluorophenyl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-chlorophenyl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-thienyl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(2-chlorophenyl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-(5-hydroxypentyl)-L-α-glutamine,
3-[(biphenyl-4-ylmethyl)amino]-3-oxopropanoic acid,
N^2-(biphenyl-4-ylcarbonyl)-N^1-propyl-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-D-α-

glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(3-pyridin-2-ylphenyl)ethyl]-L-α-glutamine,
N^2-2-naphthoyl-N^1-(3-phenylpropyl)-L-α-glutamine,
N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-[(9-oxo-9*H*-fluoren-2-yl)carbonyl]-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine,
N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-(3-phenylpropyl)-L-α-glutamine,
N^2-(4-phenoxybenzoyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-(9*H*-fluoren-2-ylcarbonyl)-N^1-hexyl-L-α-glutamine,
N^2-(9*H*-fluoren-1-ylcarbonyl)-N^1-hexyl-L-α-glutamine,
N^1-hexyl-N^2-(4-phenoxybenzoyl)-L-α-glutamine,
N^1-hexyl-N^2-[(9-oxo-9*H*-fluoren-2-yl)carbonyl]-L-α-glutamine,
N^2-[(9-oxo-9*H*-fluoren-2-yl)carbonyl]-N^1-(3-phenylpropyl)-L-α-glutamine,
N^2-(4-phenoxybenzoyl)-N^1-(3-phenylpropyl)-L-α-glutamine,
N-[4-(pyrimidin-2-ylamino)benzoyl]-L-glutamic acid,
N-(1,1'-biphenyl-4-ylcarbonyl)-D-glutamic acid,
N-[4-(pyrimidin-2-ylamino)benzoyl]-L-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-D-α-glutamine,
N^2-(1,1'-biphenyl-4-ylcarbonyl)-N^1-(4-hydroxybutyl)-L-α-glutamine,
N^1-benzyl-N^2-(1,1'-biphenyl-4-ylcarbonyl)-L-α-glutamine,
N^1-benzyl-N^2-[4-(pyrimidin-2-ylamino)benzoyl]-L-α-glutamine,
(4S)-4-[(1,1'-biphenyl-4-ylcarbonyl)amino]-5-hydroxypentanoic acid,
N-({4'-[(phenylacetyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-glutamic acid,
N-[(4'-{[(3-methyl-1-benzofuran-2-yl)carbonyl]amino}-1,1'-biphenyl-4-yl)carbonyl]-L-glutamic acid,
N-{[4'-(2-furoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid,
N-{[4'-(acetylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid,
N-{[4'-(benzoylamino)-1,1'-biphenyl-4-yl]carbonyl}-L-glutamic acid,
N-({4'-[(1-benzofuran-2-ylcarbonyl)amino]-1,1'-biphenyl-4-yl}carbonyl)-L-glutamic acid,
N^1-(1,1-dimethyl-2-phenylethyl)-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine,
N^1-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine,
N^2-(9H-fluoren-2-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine,
N^1-(6-hydroxyhexyl)-N^2-(4-phenoxybenzoyl)-L-α-glutamine,
N^2-(9H-fluoren-9-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine,
N^2-(9H-fluoren-9-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-(3-phenoxybenzoyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-(9H-fluoren-4-ylcarbonyl)-N^1-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^1-1-adamantyl-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine,
N^1-1-adamantyl-N^2-(4-phenoxybenzoyl)-L-α-glutamine,
N^1-1-adamantyl-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine,
N^1-1-adamantyl-N^2-(9H-fluoren-9-ylcarbonyl)-L-α-glutamine,
N^2-(9H-fluoren-2-ylcarbonyl)-N^1-(3-methylbenzyl)-L-α-glutamine,

N^1-(3-methylbenzyl)-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine,
N^2-(9H-fluoren-9-ylcarbonyl)-N^1-(3-methylbenzyl)-L-α-glutamine,
N^2-(9H-fluoren-2-ylcarbonyl)-N^1-propyl-L-α-glutamine,
N^1-benzyl-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine,
N^1-benzyl-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine,
N^1-benzyl-N^2-(9H-fluoren-9-ylcarbonyl)-L-α-glutamine,
N^1-benzyl-N^2-(3-phenoxybenzoyl)-L-α-glutamine,
N^1-(1-methyl-1-phenylethyl)-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine,
N^2-(9H-fluoren-9-ylcarbonyl)-N^1-(1-methyl-1-phenylethyl)-L-α-glutamine,
N^1-(1-methyl-1-phenylethyl)-N^2-(3-phenoxybenzoyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[(1S)-1-phenylethyl]-L-α-glutamine,
N^2-(9H-fluoren-2-ylcarbonyl)-N^1-[(1S)-1-phenylethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[(1S)-1-(4-fluorophenyl)ethyl]-L-α-glutamine,
tert-butyl N^2-(biphenyl-4-ylcarbonyl)-N^1-(1-phenylethyl)-L-α-glutaminate,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[(1R)-1-(4-fluorophenyl)ethyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[(1R)-1-phenylethyl]-L-α-glutamine,
N^2-(9H-fluoren-2-ylcarbonyl)-N^1-[(1R)-1-phenylethyl]-L-α-glutamine,
N^2-(9H-fluoren-1-ylcarbonyl)-N^1-(6-hydroxyhexyl)-L-α-glutamine,
N^1-(6-hydroxyhexyl)-N^2-[(9-oxo-9H-fluoren-2-yl)carbonyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-9H-fluoren-9-yl-L-α-glutamine,
N^2-(9H-fluoren-2-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-[(3'-ethoxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-[(2'-ethoxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-[(4'-methoxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-(4-bromobenzoyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-[(3'-methoxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-aα-glutamine,
4'-{[((1S)-3-carboxy-1-{[(3,4,5-trimethoxybenzyl)amino]carbonyl}propyl)amino]carbonyl}biphenyl-3-carboxylic acid,
N^2-[(4'-ethylbiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N-benzyl-N^2-[4-(2-naphthyl)benzoyl]-L-α-glutamine,
N^2-[(3',4'-dimethoxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-[(2',4'-dimethoxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N-(3,4,5-trimethoxybenzyl)-N^2-[(3',4',5'-trimethoxybiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-(1-adamantylmethyl)-N^2-(biphenyl-4-ylcarbonyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(3'-methoxybiphenyl-4-yl)carbonyl]-L-α-glutamine,

N^2-[(3',4'-dimethoxybiphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(2'-ethoxybiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(3'-fluoro-4'-methylbiphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-(4-bromobenzoyl)-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N-[(1S)-1-benzyl-2-hydroxyethyl]-N^2-(biphenyl-4-ylcarbonyl)-L-α-glutamine,
N-[(1S)-1-benzyl-2-hydroxyethyl]-N^2-(9H-fluoren-2-ylcarbonyl)-L-α-glutamine,
N-(1-adamantylmethyl)-N^2-(4-bromobenzoyl)-L-α-glutamine,
N-(1-adamantylmethyl)-N^2-[(4'-hydroxybiphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-[4-(1,3-benzodioxol-5-yl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N^2-[(2',4'-dimethoxybiphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N^2-[(3'-fluoro-4'-methylbiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N-(1-adamantylmethyl)-N^2-({4'-[(3-methoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutamine,
N-(1-adamantylmethyl)-N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-*N*-methyl-*N*-(2-phenylethyl)-L-α-glutamine,
N^2-[(4'-sec-butylbiphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-isopropylbiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-(1,1':4',1"-terphenyl-4-ylcarbonyl)-L-α-glutamine,
N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N^2-[(4'-hydroxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N-(1-adamantylmethyl)-N^2-({3'-[(dimethylamino)carbonyl]biphenyl-4-yl}carbonyl)-L-α-glutamine,
N-(1-adamantylmethyl)-N^2-[(3',5'-dimethylbiphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-(9H-fluoren-2-ylcarbonyl)-*N*-methyl-*N*-(2-phenylethyl)-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(3'-methylbiphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-({4'-[(3,5-dimethylbenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(3,4,5-trimethoxybenzyl)- L-α-glutamine,
N^2-[(4'-{[3,5-bis(trifluoromethyl)benzyl]oxy}biphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-[(3'-isopropylbiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,

N^2-[(4'-isopropylbiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N-(1-adamantylmethyl)-N^2-[4-(1-benzofuran-5-yl)benzoyl]-L-α-glutamine,
N-(1-adamantylmethyl)-N^2-[4-(1H-indol-5-yl)benzoyl]-L-α-glutamine,
N^2-[(3'-ethoxybiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(3'-methoxybiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(3'-isopropylbiphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-[(3'-fluoro-4'-methylbiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(4'-isobutylbiphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-(1,1':4',1"-terphenyl-4-ylcarbonyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N-benzyl-N^2-{[3'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-L-α-glutamine,
N-benzyl-N^2-({4'-[(3-fluorobenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutamine,
N-benzyl-N^2-{[4'-(benzyloxy)biphenyl-4-yl]carbonyl}-L-α-glutamine,
N-benzyl-N^2-[4-(phenylethynyl)benzoyl]-L-α-glutamine,
N-benzyl-N^2-{4-[(9-hydroxy-9H-fluoren-9-yl)ethynyl]benzoyl}-L-α-glutamine,
N-benzyl-N^2-{4-[(1E)-3-oxo-3-phenylprop-1-en-1-yl]benzoyl}-L-α-glutamine,
N-(3,4,5-trimethoxybenzyl)-N^2-[(2',4',6'-trimethylbiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-({4'-[(3-methoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-hydroxybiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(3'-ethoxybiphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(6-hydroxyhexyl)-L-α-glutamine,
N^2-({4'-[(3-methoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-(4-bromobenzoyl)-*N*-(3-methylbenzyl)-L-α-glutamine,
N^2-[4-(1,3-benzodioxol-5-yl)benzoyl]-*N*-(3-methylbenzyl)-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-*N*-butyl-*N*-methyl-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(4'-hydroxybiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-butyl-N^2-(9H-fluoren-2-ylcarbonyl)-*N*-methyl-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methyl-L-α-glutamine,
N^2-[4-(1,3-benzodioxol-5-yl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-[2-(3,4-dimethoxyphenyl)ethyl]-N^2-(9H-fluoren-2-ylcarbonyl)-*N*-methyl-L-α-glutamine,
N^2-(9H-fluoren-2-ylcarbonyl)-*N*-[(2R)-2-phenylpropyl]-L-α-glutamine,

N^2-(biphenyl-4-ylcarbonyl)-*N*-[(2R)-2-phenylpropyl]-L-α-glutamine,
N-benzyl-N^2-{4-[(4-hydroxycyclohexyl)ethynyl]benzoyl}-L-α-glutamine,
N^2-{4-[(3-aminophenyl)ethynyl]benzoyl}-*N*-benzyl-L-α-glutamine,
N-benzyl-N^2-[4-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)benzoyl]-L-α-glutamine,
N-benzyl-N^2-{4-[(3-methoxyphenyl)ethynyl]benzoyl}-L-α-glutamine,
N^2-[(3'-hydroxybiphenyl-4-yl)carbonyl]-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-{[4'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-methylbiphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-N^1-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-glutamamide,
N^2-({4'-[(3-tert-butylphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N^2-({4'-[(3,5-di-tert-butylphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-({4'-[(3-ethylphenoxy)methyl]biphenyl-4-yl}carbonyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-({4'-[(3-methoxyphenoxy)methyl]biphenyl-4-yl}carbonyl)-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(3'-hydroxybiphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-(biphenyl-4ylcarbonyl)-N^1-[2-(4-fluoropenyl)-1,2-dimethylethyl]-N^5-hydroxy-L-glutamanide,
N^2-[4-(5-bromo-2-thienyl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-[2-(5-chloro-2-thienyl)-1,1-dimethylethyl]-N^2-[(3'-fluorobiphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-[(3',4'-difluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(3',4'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(2',4'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(2',5'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(2',6'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(3',5'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(2',3'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-(4-pyrimidin-5-ylbenzoyl)-L-α-glutamine,
N^2-[(3',4'-difluorobiphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N^2-[(3',5'-difluorobiphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-

glutamine,
N-[2-(5-chloro-2-thienyl)-1,1-dimethylethyl]-N^2-[(3',4'-difluorobiphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-(biphenyl-4-ylcarbonyl)-*N*-[2-(5-chloro-2-thienyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-{[5-(3-chloro-4-fluorophenyl)-2-thienyl]carbonyl}-*N*-[2-(5-chloro-2-thienyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-{[4'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-{[4'-(bromomethyl)biphenyl-4-yl]carbonyl}-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[4-(2-thienyl)benzoyl]-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[4-(2-furyl)benzoyl]-L-α-glutamine,
N^2-{[4'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-*N*-(3-methylbenzyl)-L-α-glutamine,
N^2-{[3'-(hydroxymethyl)biphenyl-4-yl]carbonyl}-*N*-(3-methylbenzyl)-L-α-glutamine,
N^2-[4-(2,3-dihydro-1-benzofuran-5-yl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-[(3'-chloro-4'-fluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-{[3'-(bromomethyl)biphenyl-4-yl]carbonyl}-*N*-(3-methylbenzyl)-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[4-(3-thienyl)benzoyl]-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[4-(5-methyl-2-thienyl)benzoyl]-L-α-glutamine,
N^2-[4-(5-chloro-2-thienyl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(2-thienyl)benzoyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-{[5-(3-methoxyphenyl)-2-thienyl]carbonyl}-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(5-phenyl-2-thienyl)carbonyl]-L-α-glutamine,
N^2-(2,2'-bithien-5-ylcarbonyl)-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-[4-(2,3-dihydro-1-benzofuran-6-yl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-{[6-(3-methoxyphenyl)pyridin-3-yl]carbonyl}-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine,
N-[2-(-fluorophenyl)-1,1-dimethylethyl]-N^2-[(5-phenyl-2-thienyl)carbonyl]-L-α-glutamine,
N^2-[(3-fluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-

L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(5-pyridin-4-yl-2-thienyl)carbonyl]-L-α-glutamine,
N^2-{[5-(3-chloro-4-fluorophenyl)-2-thienyl]carbonyl}-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(2,3-dihydro-1-benzofuran-6-yl)benzoyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(5-pyridin-3-yl-2-thienyl)carbonyl]-L-α-glutamine,
N^2-[4-(2,3-dihydro-1-benzofuran-6-yl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N^2-{[5-(3-chloro-4-fluorophenyl)-2-thienyl]carbonyl}-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutaminè,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[4-(2-thienyl)benzoyl]-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-{[5-(3-methoxyphenyl)-2-thienyl]carbonyl}-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(5-phenyl-2-thienyl)carbonyl]-L-α-glutamine,
N^2-(2,2'-bithien-5-ylcarbonyl)-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(5-pyridin-4-yl-2-thienyl)carbonyl]-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(5-pyridin-3-yl-2-thienyl)carbonyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(5-chloro-2-thienyl)benzoyl]-L-α-glutamine,
N^2-{[6-(5-chloro-2-thienyl)pyridin-3-yl]carbonyl}-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-(5-phenyl-2-furoyl)-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-{[6-(5-chloro-2-thienyl)pyridin-3-yl]carbonyl}-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(6-phenylpyridin-3-yl)carbonyl]-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-{[5-(3-methoxyphenyl)-2-thienyl]carbonyl}-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-[(5-pyridin-3-yl-2-thienyl)carbonyl]-L-α-glutamine,
N^2-{[5-(3-chloro-4-fluorophenyl)-2-thienyl]carbonyl}-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-(2,2'-bithien-5-ylcarbonyl)-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(5-formyl-2-thienyl)benzoyl]-L-α-glutamine,
N^2-[4-(5-acetyl-2-thienyl)benzoyl]-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[4-(1,3-thiazol-2-yl)benzoyl]-L-α-

glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[4-(1,3-thiazol-2-yl)benzoyl]-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-(5-phenyl-2-furoyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[4-(5-formyl-2-thienyl)benzoyl]-L-α-glutamine,
N^2-[4-(5-acetyl-2-thienyl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[3-(5-chloro-2-thienyl)benzoyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[3-(2-thienyl)benzoyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-{[5-(4-chlorophenyl)-2-thienyl]carbonyl}-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-{[5-(4-fluorophenyl)-2-thienyl]carbonyl}-L-α-glutamine,
N^2-[4-(5-bromo-2-thienyl)benzoyl]-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-[4-(5-bromo-2-thienyl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-{[5-(4-fluorophenyl)-2-thienyl]carbonyl}-L-α-glutamine,
N^2-[3-(5-chloro-2-thienyl)benzoyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[3-(2-thienyl)benzoyl]-L-α-glutamine,
N^2-[(3'-chlorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-[(4'-chlorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-[(4'-fluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-[(3'-fluorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-[2-(4-chlorophenyl)-1,1-dimethylethyl]-N^2-[(3-phenyl-2-thienyl)carbonyl]-L-α-glutamine,
N^2-[(4'-chlorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-[(3'-chlorobiphenyl-4-yl)carbonyl]-*N*-[2-(4-chlorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-[2-(4-fluorophenyl)-1,1-dimethylethyl]-N^2-{[5-(4-fluorophenyl)-2-thienyl]carbonyl}-L-α-glutamine,
N^2-{[5-(4-chlorophenyl)-2-thienyl]carbonyl}-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(3-phenyl-2-thienyl)carbonyl]-L-α-glutamine,
N^2-(4-bromobenzoyl)-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-(1,1-dimethyl-2-phenylethyl)-N^2-[(4'-fluorobiphenyl-4-yl)carbonyl]-L-α-glutamine,

N-(1,1-dimethyl-2-phenylethyl)-N^2-[(3'-fluorobiphenyl-4-yl)carbonyl]-L-α-glutamine,
N^2-[4-(5-chloro-2-thienyl)benzoyl]-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-D-α-glutamine,
N^2-{[6-(5-chloro-2-thienyl)pyridin-3-yl]carbonyl}-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-{[5-(4-chlorophenyl)-2-thienyl]carbonyl}-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-{[5-(3,4-difluorophenyl)-2-thienyl]carbonyl}-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N^2-[(4'-{[3,5-bis(trifluoromethyl)phenoxy]methyl}biphenyl-4-yl)carbonyl]-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N^2-({4'-[(1,3-benzodioxol-5-yloxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(1,1-dimethyl-2-phenylethyl)-L-α-glutamine,
N^2-{[3'-(benzyloxy)biphenyl-4-yl]carbonyl}-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine, N^2-({3'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-({3'-[(3-methoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-(3,4,5-trimethoxybenzyl)-L-α-glutamine,
N^2-({4'-[(3,5-dimethoxybenzyl)oxy]biphenyl-4-yl}carbonyl)-*N*-[2-(4-fluorophenyl)-1,1-dimethylethyl]-L-α-glutamine,
N-benzyl-N^2-{[4'-(biphenyl-3-ylmethoxy)biphenyl-4-yl]carbonyl}-L-α-glutamine,
N-benzyl-N^2-({4'-[(3'-methoxybiphenyl-3-yl)methoxy]biphenyl-4-yl}carbonyl)-L-α-glutamine,
N^2-({4'-[(3,5-dimethoxyphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(3-methylbenzyl)-L-α-glutamine,
N^2-({3'-[(3,5-dimethoxyphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(3-methylbenzyl)-L-α-glutamine,
N^2-[(3'-{[3,5-bis(trifluoromethyl)phenoxy]methyl}biphenyl-4-yl)carbonyl]-*N*-(3-methylbenzyl)-L-α-glutamine,
N^2-({3'-[(3-ethylphenoxy)methyl]biphenyl-4-yl}carbonyl)-*N*-(3-methylbenzyl)-L-α-glutamine,
N-benzyl-N^2-{[4'-(biphenyl-2-ylmethoxy)biphenyl-4-yl]carbonyl}-L-α-glutamine, or
N-benzyl-N^2-({4'-[(3'-methoxybiphenyl-2-yl)methoxy]biphenyl-4-yl}carbonyl)-L-α-glutamine.

22. A method of modulating the activity of a metalloproteinase in an animal in need thereof comprising contacting the metalloproteinase with an effective amount of a compound or salt claimed in any one of claims 1 to 21.

23. The method of claim 22, wherein the metalloproteinase is a matrix metalloproteinase or an aggrecanase.

24. The method of claim 23, wherein the aggrecanase is aggrecanase-1 or aggrecanase-2.

25. A composition comprising an effective amount of the compound or a pharmaceutically acceptable salt of the compound as claimed in any one of claims 1 to 21 and a pharmaceutically acceptable carrier.

26. The composition of claim 25, wherein the pharmaceutically acceptable carrier is suitable for oral administration and the composition comprises an oral dosage form.

27. A method for treating a metalloproteinase-related disorder, in an animal in need thereof, which comprises, administering an effective dose of the compound as claimed in any one of claims 1 to 21, or a pharmaceutically acceptable salt or hydrate thereof.

28. The method of claim 27, wherein the metalloproteinase is a matrix metalloproteinase or an aggrecanase.

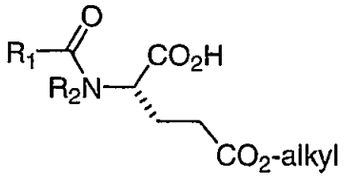
29. The method of claim 28, wherein the aggrecanase is aggrecanase-1 or aggrecanase-2.

30. The method of claim 27, wherein the metalloproteinase-related disorder is selected from the group consisting of arthritic disorders, osteoarthritis, cancer, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, atherosclerosis, age-related macular degeneration, myocardial infarction, corneal ulceration and other ocular surface diseases, hepatitis, aortic aneurysms, tendonitis, central nervous system diseases, abnormal wound healing, angiogenesis, restenosis, cirrhosis, multiple sclerosis, glomerulonephritis, graft versus host disease, diabetes, inflammatory bowel disease, shock, invertebral disc degeneration, stroke, osteopenia, and periodontal diseases.

31. The method of claim 30, wherein the metalloproteinase-related disorder is osteoarthritis.

32. A method of synthesizing a compound comprising:

a) treating a compound of the formula (III):



(III)

wherein

R_1 is phenyl, heteroaryl, biphenyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each optionally substituted with one or more of R_5 or R_6, and when R_1 is substituted with more than one of R_5 or R_6, the substituents can be identical or different;

R_2 is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -$(CH_2)_nR_{11}$, -OH, or -O-(C_1-C_6) alkyl;

R_5 is aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, -CO-(C_1-C_6) alkyl, -CO-aryl, -CO-heteroaryl, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2NH-aryl, -SO_2NH-heteroaryl, -$NHSO_2$-(C_1-C_6) alkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl, -CONH-heteroaryl, (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, or -CONH-(C_3-C_6) cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different;

R_6 is hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6) alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6)

alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

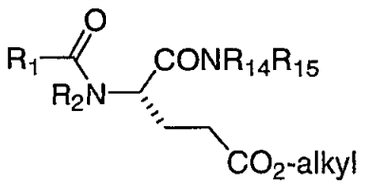
R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_{11} is aryl, heteroaryl, or cycloalkyl;

R_{13} is halogen, -O-(C_1-C_6) alkyl, -CO_2H, -OH, -CF_3, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl substituted with -OH, aryl substituted with -NH_2, aryl substituted with -O-(C_1-C_6) alkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; and

n is 0-4;

with an amine, under conditions effective to provide a compound having the formula (IV):



(IV);

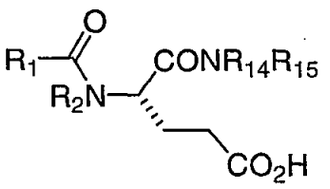
wherein

R_{14} and R_{15} are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, heterocycloalkyl -$(CH_2)_n$-aryl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_{14} and R_{15} together may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S; and

R_{12} is hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8,

$-CONR_7R_8$, $-NR_8COR_7$, $-NR_8CO_2R_7$, $-CO_2R_7$, $-COR_7$, $-SO_2-(C_1-C_6)$ alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl, $-SO_2R_7$, $-NR_7SO_2R_8$, $-SO_2NR_7R_8$; linear or branched or cyclic (C_1-C_6) alkyl, $-O-(C_1-C_6)$ alkyl, $-S-(C_1-C_6)$ alkyl, or $-NH-(C_1-C_6)$ alkyl; heterocycloalkyl, $-(C_1-C_6)$ alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, $-O-(C_1-C_6)$ alkyl cycloalkyl, -O-alkenyl, $-O-(C_1-C_6)$ alkyl aryl, aryl, heteroaryl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl, each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13}; and

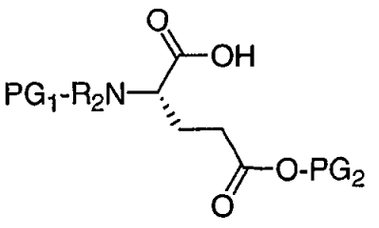
b) treating the compound of the formula (IV) under conditions effective for hydrolysis of the alkyl ester, thereby providing a compound having the formula (II):



(II).

33. A method of synthesizing a compound comprising:

a) treating a compound of the formula (V):



(V)

wherein

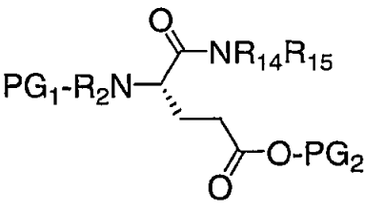
PG_1 is an amine protecting group and PG_2 is a carboxylic acid protecting group;

R_2 is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, $-(CH_2)_nR_{11}$, -OH, or $-O-(C_1-C_6)$ alkyl;

R_{11} is aryl, heteroaryl, or cycloalkyl; and

n is 0-4;

with an amine, under conditions effective to provide a compound having the formula (VI):



(VI)

wherein

R_{14} and R_{15} are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, heterocycloalkyl -$(CH_2)_n$-aryl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_{14} and R_{15} together may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

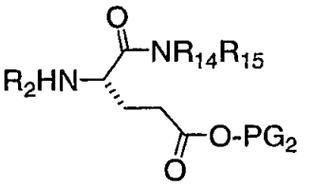
R_{12} is hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6) alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached

may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S; and

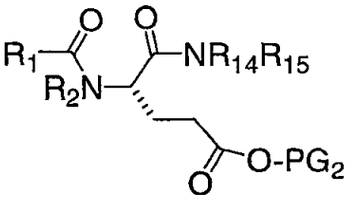
R_{13} is halogen, -O-(C_1-C_6) alkyl, -CO_2H, -OH, -CF_3, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl substituted with -OH, aryl substituted with -NH_2, aryl substituted with -O-(C_1-C_6) alkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl;

b) hydrolyzing the amine protecting group of a compound of the formula (VI), under conditions effective to provide a compound having the formula (VII):



(VII);

c) treating the compound of the formula (VII) with a carboxylic acid, under conditions effective to provide a compound having the formula (VIII):



(VIII);

wherein

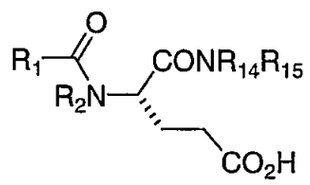
R_1 is phenyl, heteroaryl, biphenyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each optionally substituted with one or more of R_5 or R_6, and when R_1 is substituted with more than one of R_5 or R_6, the substituents can be identical or different;

R_5 is aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, -CO-(C_1-C_6) alkyl, -CO-aryl, -CO-heteroaryl, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2NH-aryl, -SO_2NH-heteroaryl, -$NHSO_2$-(C_1-C_6) alkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl,

-CONH-heteroaryl, (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, or -CONH-(C_3-C_6) cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different; and

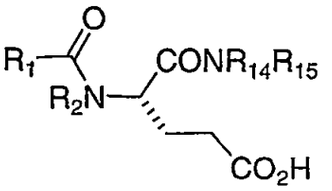
R_6 is hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6) alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13}; and

d) treating the compound of the formula (VIII) under conditions effective for hydrolysis of the protected carboxylic acid, thereby providing a compound having the formula (II):



(II).

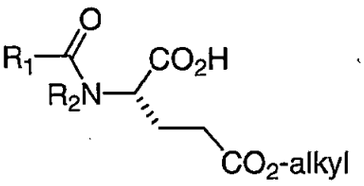
34. A compound of the formula (II):



(II);

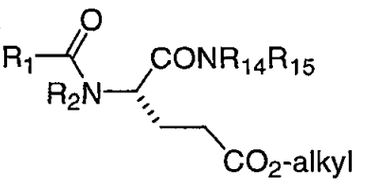
prepared by the method comprising:

a) treating a compound of the formula (III):



(III)

with an amine, under conditions effective to provide a compound having the formula (IV):



(IV);

b) treating the compound of the formula (IV) under conditions effective for hydrolysis of the alkyl ester, thereby providing a compound having the formula (II);

wherein

R_1 is phenyl, heteroaryl, biphenyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each optionally substituted with one or more of R_5 or R_6, and when R_1 is substituted with more than one of R_5 or R_6, the substituents can be identical or different;

R_2 is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -$(CH_2)_nR_{11}$, -OH, or -O-(C_1-C_6) alkyl;

R_5 is aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, -CO-(C_1-C_6) alkyl, -CO-aryl, -CO-heteroaryl, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl,

-SO_2NH-aryl, -SO_2NH-heteroaryl, -$NHSO_2$-(C_1-C_6) alkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl, -CONH-heteroaryl, (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, or -CONH-(C_3-C_6) cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different;

R_6 and R_{12} are each independently hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6) alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_{11} is aryl, heteroaryl, or cycloalkyl;

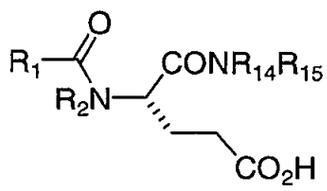
R_{13} is halogen, -O-(C_1-C_6) alkyl, -CO_2H, -OH, -CF_3, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl substituted with -OH, aryl substituted with -NH_2, aryl substituted with -O-(C_1-C_6) alkyl,

-$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl;

R_{14} and R_{15} are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, heterocycloalkyl -$(CH_2)_n$-aryl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_{14} and R_{15} together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S; and

n is 0-4.

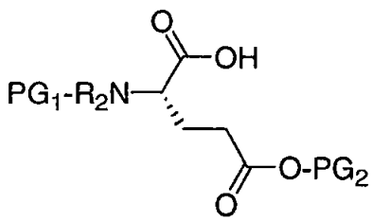
35. A compound of the formula (II):



(II);

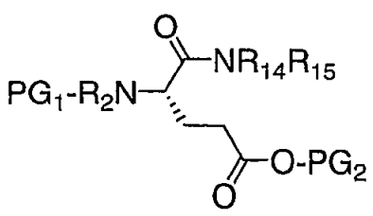
prepared by the method comprising:

a) treating a compound of the formula (V):



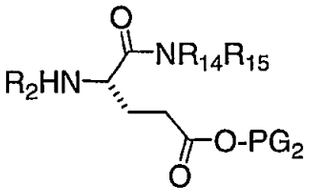
(V)

with an amine, under conditions effective to provide a compound having the formula (VI):



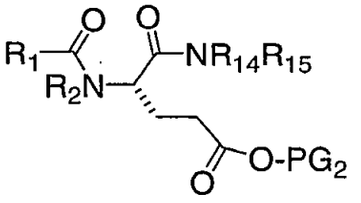
(VI);

b) hydrolyzing the amine protecting group of a compound of the formula (VI), under conditions effective to provide a compound having the formula (VII):



(VII);

c) treating the compound of the formula (VII) with a carboxylic acid, under conditions effective to provide a compound having the formula (VIII):



(VIII);

d) treating the compound of the formula (VIII) under conditions effective for hydrolysis of the protected carboxylic acid, thereby providing a compound having the formula (II);

wherein

PG_1 is an amine protecting group and PG_2 is a carboxylic acid protecting group;

R_1 is phenyl, heteroaryl, biphenyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each optionally substituted with one or more of R_5 or R_6, and when R_1 is substituted with more than one of R_5 or R_6, the substituents can be identical or different;

R_2 is hydrogen, $(C_1\text{-}C_6)$ alkyl, $(C_2\text{-}C_6)$ alkenyl, $(C_2\text{-}C_6)$ alkynyl, $-(CH_2)_nR_{11}$, -OH, or $-O\text{-}(C_1\text{-}C_6)$ alkyl;

R_5 is aryl, heteroaryl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, -S-heteroaryl, -NH-aryl, -NH-heteroaryl, $-CO\text{-}(C_1\text{-}C_6)$ alkyl, -CO-aryl, -CO-heteroaryl, $-SO_2\text{-}(C_1\text{-}C_6)$ alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl, $-SO_2NH$-aryl, $-SO_2NH$-heteroaryl, $-NHSO_2\text{-}(C_1\text{-}C_6)$ alkyl, $-NHSO_2$-aryl, $-NHSO_2$-heteroaryl, -NHCO-aryl, -NHCO-heteroaryl, -CONH-aryl,

-CONH-heteroaryl, (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, or -CONH-(C_3-C_6) cycloalkyl; each alkyl, aryl, cycloalkyl, or heteroaryl optionally substituted with one or more of R_6, and when R_5 is substituted with more than one R_6, the substituents can be identical or different;

R_6 and R_{12} are each independently hydrogen, halogen, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-(C_1-C_6) alkyl, -SO_2-aryl, -SO_2-heteroaryl, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; (C_1-C_6) alkyl, -O-(C_1-C_6) alkyl, -S-(C_1-C_6) alkyl, -NH-(C_1-C_6) alkyl, -NHCO-(C_1-C_6) alkyl, -CONH-(C_1-C_6) alkyl, -O-(C_3-C_6) cycloalkyl, -S-(C_3-C_6) cycloalkyl, -NH-(C_3-C_6) cycloalkyl, -NHCO-(C_3-C_6) cycloalkyl, -CONH-(C_3-C_6) cycloalkyl, heterocycloalkyl, -(C_1-C_6) alkyl-OR_7, (C_2-C_6) alkynyl, (C_2-C_6) alkenyl, -O-(C_1-C_6) alkyl-(C_3-C_6) cycloalkyl, -O-alkenyl, -O-(C_1-C_6) alkyl substituted with aryl, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, -O-aryl, -O-heteroaryl, -S-aryl, or -S-heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkenyl, or alkynyl optionally substituted with one or more of R_{13};

R_7 and R_8 are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl; or R_7 and R_8 together with the atom to which they are attached may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S;

R_{11} is aryl, heteroaryl, or cycloalkyl;

R_{13} is halogen, -O-(C_1-C_6) alkyl, -CO_2H, -OH, -CF_3, hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, cycloalkyl substituted with -OH, aryl substituted with -NH_2, aryl substituted with -O-(C_1-C_6) alkyl, -$(CH_2)_n$-aryl, or -$(CH_2)_n$-heteroaryl;

R_{14} and R_{15} are each independently hydrogen, (C_1-C_6) alkyl, aryl, heteroaryl,

(C_2-C_6) alkenyl, (C_2-C_6) alkynyl, cycloalkyl, heterocycloalkyl -$(CH_2)_n$-aryl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl; each alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl optionally substituted with one or more R_{12}; or R_{14} and R_{15} together may form a five- to seven-membered cyclic group containing up to 3 heteroatoms selected from N, O, or S; and

n is 0-4.

Figure 1: Inhibition of aggrecan degradation by test compound 8OO

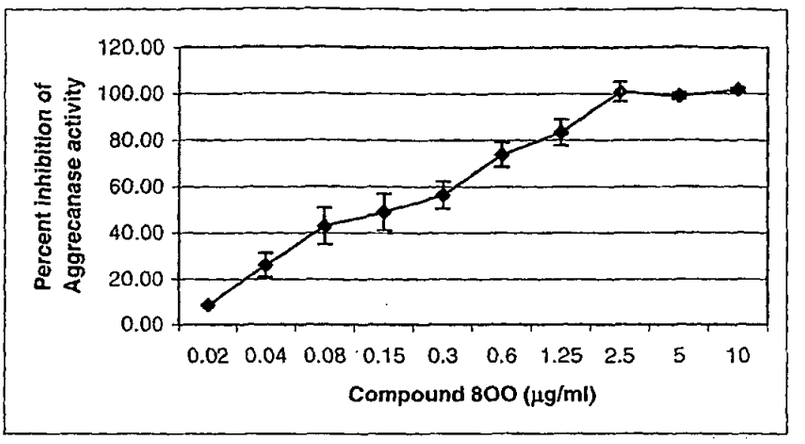
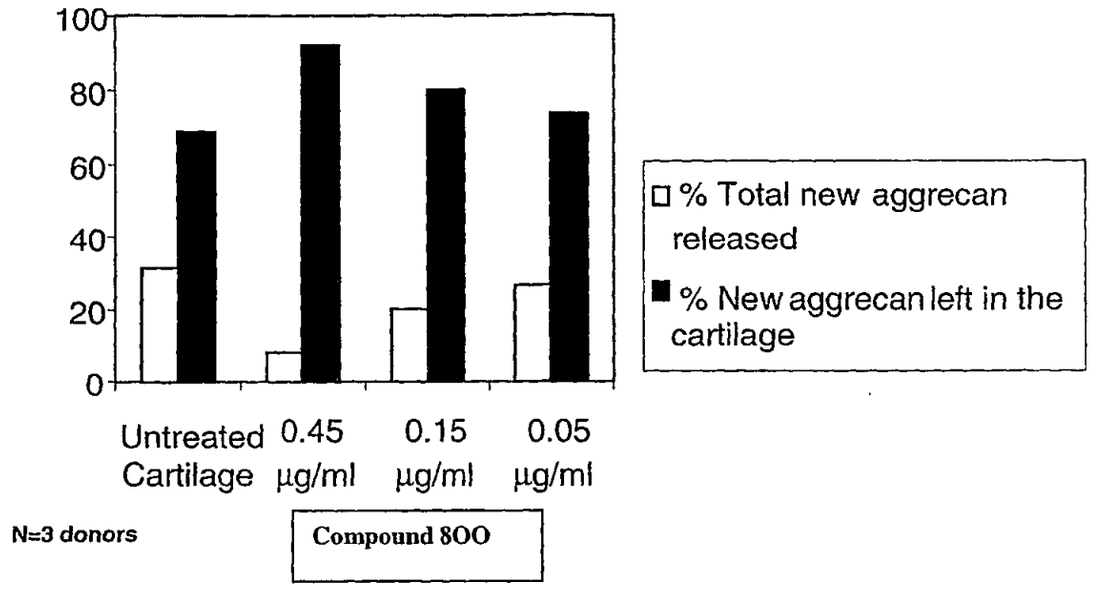


Figure 2: Test compound 8OO and Aggrecan metabolism



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INHIBIDORES DE AGRECANASA GLUTAMATO

A través de esta solicitud, se hacen varias referencias a publicaciones. La descripción de estas publicaciones en su totalidad se incorpora como referencia en esta solicitud con el fin de describir más completamente el estado de la técnica como se conoce por aquellos expertos hasta la fecha de la invención descrita y reivindicada aquí.

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Solicitud relacionada

Esta solicitud reivindica el beneficio de acuerdo con el 35 U.S.C. § 119(e) de la solicitud provisional U.S. No. 60/697,590 presentada en Julio 11, 2005, que se incorpora aquí como referencia en su totalidad.

Campo de la invención

La presente invención se relaciona con compuestos y su uso como, por ejemplo, inhibidores de metaloproteinasa.

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Antecedente de la invención

Las metaloproteinasas, que incluyen metaloproteinasas de matriz y agrecanasas, se conocen por tener un papel en la descomposición del tejido conectivo. La matriz de metaloproteinasas ("MMP") constituye una súperfamilia de enzimas proteolíticas que se relacionan genéticamente y son capaces de degradar casi todos los constituyentes de matriz extracelular y membrana base que restringe el movimiento celular. Las agrecanasas son membranas de la familia de proteínas ADAMTS (una disintegrina y metaloproteinasa con motivos trombospondin). La agrecanasa-1 y agrecanasa-2 se han designado ADAMTS-4 y ADAMTS-5, respectivamente (Tang BL, Int J Biochem Cell Biol 2001, 33, 33-44).

La familia ADAMTS está involucrada en la segmentación del agrecán, un compuesto de cartílago también conocido como el gran agregado de proteoglicano de sulfato de condroitina (Abbaszade I et al., J Biol Chem 1999, 274, 23443-23450), procesamiento de procolágeno (Colige A et al., Proc Natl Acad Sd USA 1997, 94, 2374-2379), angiogénesis (Vazquez F et al., J Biol Chem 1999, 274, 23349-23357), inflamación (Kuno K et al., J Biol Chem 1997, 272, 556-562) e invasión de tumor (Masui T. et al., J Biol Chem 1997, 272, 556- 562). El MMP también ha mostrado segmentar el agrecán.

La pérdida de agrecán ha estado implicada en la degradación del cartílago articular en enfermedades artríticas, por

ejemplo la osteoartrítis es una enfermedad debilitante que afecta por lo menos treinta millones de americanos. La degradación del cartílago articular y el dolor crónico resultante pueden reducir severamente la calidad de vida. Una característica importante y prematura del proceso osteoartrítico es la pérdida de agrecán de la matriz extracelular, que resultan en deficiencias en las características biomecánicas del cartílago. De la misma manera, el MMP y las agrecanasas se conocen por jugar un papel en muchos trastornos en los que ocurre la destrucción o degradación de la proteína extracelular, tal como cáncer, asma, enfermedad pulmonar obstructiva crónica ("COPD"), aterosclerosis, degeneración macular relacionada con la edad, infarto del miocardio, ulceración de córnea y otras enfermedades de superficie ocular, hepatitis, aneurismas aórticas, tendonitis, enfermedades del sistema nervioso central, cicatrización anormal de heridas, angiogénesis, reestenosis, cirrosis, esclerosis múltiple, glomerulonefritis, enfermedad de anfitrión Vs. Injerto, diabetes, enfermedad inflamatoria del intestino, choque, degeneración de disco intervertebral, apoplejía, osteopenia, y enfermedades periodontales.

Por lo tanto, los inhibidores de metaloproterinasa, que incluyen inhibidores de MMP y agrecanasas, son necesarios.

La presente invención se dirige a estos y otros fines importantes.

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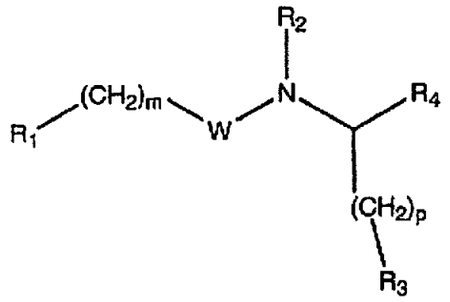
Resumen de la invención

En una modalidad, la invención proporciona compuestos de la Fórmula (I):



(I)

y sales farmacéuticamente aceptables de estos,

en donde

W es -C(O)-, -OC(O)-, -NHC(O)-, -C(O)O-, o -C(O)NH-;

R_1 es fenilo, heteroarilo, bifenilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada uno se sustituye opcionalmente con uno o más de R_5 o R_6, y cuando R_1 se sustituye con más de uno de R_5 o R_6, los sustituyentes pueden ser idénticos o diferentes;

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), $-(CH_2)_nR_{11}$, -OH, o -O-alquilo (C_1-C_6);

R_3 es $-CO_2H$, $-CONH_2$, -CONHOH, $-CONHSO_2R_7$, tetrazol, $-SO_2NHR_7$, $-SO_3H$, $-PO(OH)NH_2$, $-PO(OH)OR_7$, $-CONHR_7$, $-COOR_7$, un grupo de

ácido mimético, o un heterocicloalquilo de 5 o 6 miembros o heteroarilo que contiene 1 a 4 heteroátomos seleccionados de O, N, S;

R_4 es $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, o $-CONR_9R_{10}$;

R_5 es arilo, heteroarilo, $-(CH_2)_n$-arilo, $-(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, -S-heteroarilo, -NH-arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO-arilo, -CO-heteroarilo, $-SO_2$-alquilo (C_1-C_6), $-SO_2$-arilo, $-SO_2$-heteroarilo, $-SO_2NH$-arilo, $-SO_2NH$-heteroarilo, $-NHSO_2$-alquilo (C_1-C_6), $-NHSO_2$-arilo, $-NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R_5 se sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes;

R_6 y R_{12} son cada uno independientemente hidrógeno, halógeno, -CN, $-OCF_3$, $-CF_3$, $-NO_2$, -OH, -SH, $-NR_7R_8$, $-CONR_7R_8$, $-NR_8COR_7$, $-NR_8CO_2R_7$, $-CO_2R_7$, $-COR_7$, $-SO_2$-alquilo (C_1-C_6), $-SO_2$-arilo, $-SO_2$-heteroarilo, $-SO_2R_7$, $-NR_7SO_2R_8$, $-SO_2NR_7R_8$, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo

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(C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo, $-(CH_2)_n$-arilo, $-(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_9 y R_{10} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), alquilo (C_1-C_6)-OH, alquilo (C_1-C_6)-O-alquilo (C_1-C_6), arilo, cicloalquilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más R_{12}; o R_9 y R_{10} juntos pueden formar un grupo cíclico de

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cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_{11} es arilo, heteroarilo, o cicloalquilo;

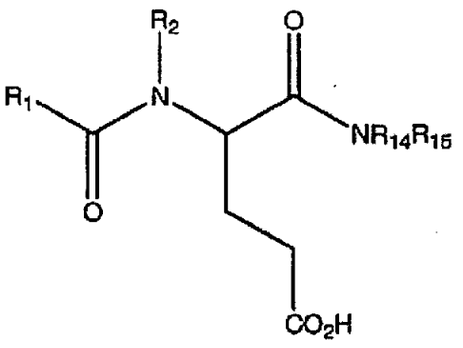
R_{13} es halógeno, -O-alquilo (C_1-C_6), -CO_2H, -OH, -CF_3, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con -NH_2, arilo sustituido con -O-alquilo (C_1-C_6), -$(CH_2)_n$-arilo, o -$(CH_2)_n$-heteroarilo;

m es 0-4;

n es 0-4; y

p es 0-2.

En otra modalidad, la invención proporciona compuestos de la Fórmula (II):



(II)

y sales farmacéuticamente aceptables de estos,

en donde

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), $-(CH_2)_pR_{11}$, -OH, o -O-alquilo (C_1-C_6);

R_{14} y R_{15} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, heterocicloalquil-$(CH_2)_n$-arilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más R_{12}; o R_{14} y R_{15} juntos pueden formar un grupo cíclico de cinco- a siete-miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

p es 0-2, y

R_1, R_{11}, R_{12}, y n son como se describió anteriormente para los compuestos de la Fórmula (I).

En otra modalidad, los compuestos o sales farmacéuticamente aceptables de los compuestos de Fórmula (I) o Fórmula (II) son útiles como composiciones farmacéuticas que comprenden compuestos o sales farmacéuticamente aceptables de compuestos de Fórmula (I) o Fórmula (II) y un portador farmacéuticamente aceptable.

En una modalidad, los compuestos o sales farmacéuticamente aceptables de los compuestos de la Fórmula (I) o Fórmula (II) son útiles como moduladores de metaloproteinasa.

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En una modalidad, la invención proporciona métodos para tratar un trastorno relacionado con metaloproteinasa, que comprende administrar a un animal en necesidad de estos los compuestos o sales farmacéuticamente aceptables de compuestos de Fórmula (I) o Fórmula (II) en una cantidad efectiva para tratar un trastorno relacionado con metaloproteinasa.

En una modalidad, la invención proporciona métodos para sintetizar los compuestos o sales farmacéuticamente aceptables de compuestos de Fórmula (I) o Fórmula (II). En otra modalidad, la invención proporciona compuestos o sales farmacéuticamente aceptables de compuestos de Fórmula (I) o Fórmula (II) hechos por procesos particulares.

Descripción de la Invención

Todas las relaciones de un grupo, tal como alquilo, se entienden para los propósitos de esta especificación que abarca ambas formas sustituidas y no sustituidas.

El término "alquilo", como se utiliza aquí, si se utiliza solo o como parte de otro grupo, se refiere a una cadena de hidrocarburo alifático sustituido o no sustituido e incluye, pero no se limita a, cadenas rectas y ramificadas que contienen de 1 a 12 átomos de carbono, o en algunos casos, de 1 a 6 átomos de carbono, a menos que se especifique explícitamente de otra forma. Por ejemplo, metilo, etilo, propilo, isopropilo, butilo, i-butilo y t-butilo se abarcan por el término "alquilo." alquilo (C_1-C_6) incluye grupos

alifáticos de cadena recta o ramificada que tienen de 1 a 6 carbonos. Específicamente incluidos dentro de la definición de "alquilo" están aquellas cadenas de hidrocarburo alifáticas que se sustituyen opcionalmente. El alquilo puede ser adecuadamente a un alquilo (C_1-C_3). En una modalidad, un alquilo se sustituye opcionalmente con uno o más de los siguientes grupos: -halógeno, $-N(R')_2$, metilenodioxo, etilenodioxo, - $NHSO_2R'$, $-NR'COR'$, $-NHCO_2R'$, $-NO_2$, $-SO_2N(R')_2$, $-SO_2R'$, $-OR'$, $-COR'$, $-CO_2R'$, - $CON(R')_2$, o -CN, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido, o arilo no sustituido.

El número de carbonos como se utiliza en las definiciones aquí se refieren a estructura principal de carbono y ramificaciones de carbono, pero no incluye los átomos de carbono de los sustituyentes, tal como sustituciones alcoxi y similares.

El término "alquenilo", como se utiliza aquí, si se utiliza solo o como parte de otro grupo, se refiere a una cadena de hidrocarburo sustituida o no sustituida e incluye, pero no se limita a, cadenas rectas y ramificadas que tienen de 2 a 8 átomos de carbono por ejemplo 2 a 6 átomos de carbono y que contiene por lo menos un enlace doble. En una modalidad, la porción alquenilo tiene 1 o 2 enlaces dobles. Tales porciones alquenilo pueden existir en las conformaciones E o Z y los compuestos de esta invención incluyen ambas conformaciones. Alquenilo (C_2-C_6) incluye a una cadena recta o ramificada de 2 a 6 carbonos que tiene por lo menos un enlace doble carbono-

carbono. Específicamente incluidos dentro de la definición de "alquenilo" están aquellas cadenas de hidrocarburo alifáticas que se sustituyen opcionalmente. En una modalidad, un heteroátomo, tal como O, S o N, adherido a un alquenilo no está adherido a un átomo de carbono que se une a un enlace doble. En una modalidad, un alquenilo se sustituye opcionalmente con uno o más de los siguientes grupos: -halógeno, $-N(R')_2$, metilenodioxo, etilenodioxo, $-NHSO_2R'$, $-NR'COR'$, $-NHCO_2R'$, $-NO_2$, $-SO_2N(R')_2$, $-SO_2R'$, $-OR'$, $-COR'$, $-CO_2R'$, $-CON(R')_2$, o $-CN$, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido, o arilo no sustituido.

El término "alquinilo", como se utiliza aquí, si se utiliza solo o como parte de otro grupo, se refiere auna porción hidrocarburo que contiene por lo menos un enlace triple carbono-carbono. Alquinilo (C_2-C_6) incluye una cadena recta o ramificada de 2 a 6 carbonos que tiene por lo menos un enlace triple carbono-carbono. En una modalidad, un alquinilo se sustituye opcionalmente con uno o más de los siguientes grupos: -halógeno, $-N(R')_2$, metilenodioxo, etilenodioxo, $-NHSO_2R'$, $-NR'COR'$, $-NHCO_2R'$, $-NO_2$, $-SO_2N(R')_2$, $-SO_2R'$, $-OR'$, $-COR'$, $-CO_2R'$, $-CON(R')_2$, o $-CN$, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido, o arilo no sustituido.

El término "cicloalquilo" se refiere a un sistema de anillo de hidrocarburo no aromático saturado o insaturado monovalente monocíclico, bicíclico, tricíclico, fusionado,

puenteado o espiro de 3-15 átomos de carbono por ejemplo 3 a 6 átomos de carbono. Cualquier posición de anillo adecuada de la porción cicloalquilo se puede ligar covalentemente a la estructura química definida. Ejemplos de porciones cicloalquilo incluyen, pero no se limitan a, ciclopropilo, ciclopropilmetilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, norbornilo, adamantilo, espiro[4.5]decanilo, y homólogos, isómeros, y similares. El cicloalquilo C_3-C_6 incluye anillo saturados, monocíclicos de 3 a 6 carbonos. En una modalidad, un cicloalquilo se sustituye opcionalmente con uno o más de los siguientes grupos: -V-halógeno, -alquilo (C_1-C_6), -alquenilo (C_2-C_6), -alquinilo (C_2-C_6), -V-N(R')$_2$, metilenodioxo, etilenodioxo, -V- $NHSO_2R'$, -V-NR'COR', -V-$NHCO_2R'$, -V-NO_2, -V-$SO_2N(R')_2$, -V-SO_2R', -V-OR', -V-COR', -V-CO_2R', -V-$CON(R')_2$, o -V-CN, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido, o arilo no sustituido; y en donde cada V es independientemente un enlace o alquilo (C_1-C_6). Cicloalquilalquilo cuando se utiliza aquí se refiere a un grupo alquilo (C_1-C_6) como se definió anteriormente sustituido por un grupo cicloalquilo C_3 a C_{15} como se definió anteriormente, por ejemplo ciclohexilmetilo y ciclohexiletilo.

"Heteroarilo" se refiere a un anillo heterocíclico aromático de 5 a 6 miembros que contiene de 1 a 4 heteroátomos seleccionados del grupo que consiste de átomos de oxígeno, nitrógeno, y azufre en el anillo, y a la que se puede fusionar con un anillo carbocíclico o heterocíclico en cualquier posición posible (por ejemplo fusionado a uno o más

anillos carbocíclicos o heterocíclicos, cada uno tiene 5-8 átomos en el anillo, el anillo heterocíclico fusionado contiene de 1 a 4 heteroátomos seleccionados del grupo que consiste de átomos de oxígeno, nitrógeno, y azufre en el anillo), por ejemplo este es adecuadamente un anillo bicíclico o tricíclico. Grupos heteroarilo de ejemplo incluyen, pero no se limitan a, furanilo, furazanilo, homopiperazinilo, imidazolinilo, isotiazolilo, isoxazolilo, oxadiazolilo, oxazolilo, pirimidinilo, fenantridinilo, piranilo, pirazinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridinilo, pirimidinilo, pirrolinilo, tiadiazinilo, tiadiazolilo, tienilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tiofenilo, triazinilo, y triazolilo. En una modalidad, un heteroarilo se sustituye opcionalmente con uno o más de los siguientes grupos: -V-halógeno, -alquilo (C_1-C_6), -alquenilo (C_2-C_6), -alquinilo (C_2-C_6), -V-N(R')$_2$, metilenodioxo, etilenodioxo, -V-NHSO$_2$R', -V-NR'COR', -V-NHCO$_2$R', -V-NO$_2$, - V-SO$_2$N(R')$_2$, -V-SO$_2$R', -V-OR', -V-COR', -V-CO$_2$R', -V-CON(R')$_2$, o -V-CN, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido o arilo no sustituido; y en donde cada V es independientemente un enlace o alquilo (C_1-C_6).

"Heterocicloalquilo" se refiere a un anillo no aromático saturado o insaturado de 5 a 7-miembros que contiene átomos de carbono y de 1 a 4 heteroátomos seleccionados de N, O, y S que puede ser adecuadamente monocíclico o se puede fusionar a uno o más anillos adicionales para proporcionar una porción

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policíclica por ejemplo una porción bicíclica o tricíclica. El anillo o anillos adicionales pueden ser anillo o anillos carbocíclicos o ellos pueden contener de 1 a 4 heteroátomos adicionales seleccionados de N, O y S, preferiblemente ellos son anillos carbocíclicos. El anillo o anillo adicionales pueden ser anillo o anillos aromáticos, saturados o insaturados, preferiblemente ellos son anillos no aromáticos. Grupos heterocicloalquilo de ejemplo incluyen, pero no se limitan a, azepanilo, azetidinilo, aziridinilo, imidazolidinilo, morfolinilo, oxazolidinilo, oxazolidinilo, piperazinilo, piperidinilo, pirazolidinilo, pirrolidinilo, quinuclidinilo, tetrahidrofuranilo, y tiomorfolinilo. En una modalidad, un heterocicloalquilo se sustituye opcionalmente con uno o más de los siguientes: -V-halógeno, -alquilo (C_1-C_6), -alquenilo (C_2-C_6), -alquinilo (C_2-C_6), -V-$N(R')_2$, metilenodioxo, etilenodioxo, -V-$NHSO_2R'$, -V-$NR'COR'$, -V-$NHCO_2R'$, -V-NO_2, - V-$SO_2N(R')_2$, -V-SO_2R', -V-OR', -V-COR', -V-CO_2R', -V-$CON(R')_2$, o -V-CN, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido o arilo no sustituido; y en donde cada V es independientemente un enlace o alquilo (C_1-C_6).

El término "arilo" como se utiliza aquí como un grupo o parte de un grupo se refiere a un sistema de anillo carbocíclico aromático, por ejemplo, de 6 a 14 átomos de carbono tal como fenilo, que se puede sustituir opcionalmente. Un grupo arilo se puede fusionar con un anillo carbocíclico o heterocíclico en cualquier posición posible (por ejemplo fusionado a uno o más anillos carbocíclicos o heterocíclicos, cada uno tiene 5-

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8 átomos en el anillo, el anillo heterocíclico fusionado contiene de 1 a 4 heteroátomos seleccionados del grupo que consiste de átomos de oxígeno, nitrógeno, y azufre en el anillo). "Fenilo", como se utiliza aquí, si se utiliza solo o como parte de otro grupo, se refiere a un grupo fenilo sustituido o no sustituido. El arilo fusionado con un anillo carbocíclico puede ser adecuadamente un arilo bicíclico o un arilo tricíclico. En una modalidad, un grupo arilo tal como fenilo se sustituye opcionalmente con uno o más de los siguientes: - V-halógeno, alquilo (C_1-C_6), -alquenilo (C_2-C_6), -alquinilo (C_2-C_6), -V-$N(R')_2$, metilenodioxo, etilenodioxo, -V-$NHSO_2R'$, -V-$NR'COR'$, -V-$NHCO_2R'$, -V-NO_2, - V-$SO_2N(R')_2$, -V-SO_2R', -V-OR', -V-COR', -V-CO_2R', -V-$CON(R')_2$, o -V-CN, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido, o arilo no sustituido; y en donde cada V es independientemente un enlace o alquilo (C_1-C_6).

El término "bifenilo" como se utiliza aquí se refiere a dos grupos fenilo conectados a un sitio de carbono en cada anillo. En una modalidad, uno o ambos grupos fenilo son independientemente se sustituye opcionalmente con uno o más de los siguientes grupos: -V- halógeno, - alquilo (C_1-C_6), -alquenilo (C_2-C_6), -alquinilo (C_2-C_6), -V-$N(R')_2$, metilenodioxo, etilenodioxo, -V-$NHSO_2R'$, -V-$NR'COR'$, -V-$NHCO_2R'$, -V-NO_2, -V-$SO_2N(R')_2$, -V-SO_2R', -V-OR', -V-COR', -V-CO_2R', -V-$CON(R')_2$, o -V-CN, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido, o arilo no sustituido; y en donde cada V es independientemente un enlace o alquilo (C_1-C_6).

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El término "biarilo" como se utiliza aquí se refiere a dos grupos arilo conectados a un sitio de carbono en cada anillo. En una modalidad, uno o ambos grupos arilo son independientemente se sustituye opcionalmente con uno o más de los siguientes grupos: -V-halógeno, -alquilo (C_1-C_6), -alquenilo (C_2-C_6), -alquinilo (C_2-C_6), -V-$N(R')_2$, metilenodioxo, etilenodioxo, -V-$NHSO_2R'$, -V-$NR'COR'$, -V-$NHCO_2R'$, -V-NO_2, -V-$SO_2N(R')_2$, -V-SO_2R', -V-OR', -V-COR', -V-CO_2R', -V-$CON(R')_2$, o -V-CN, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido, o arilo no sustituido; y en donde cada V es independientemente un enlace o alquilo (C_1-C_6).

El término "arilo bicíclico" como se utiliza aquí se refiere a dos grupos carbocíclicos fusionados, en donde uno o ambos de los grupos carbocíclicos es aromático. Por ejemplo, un arilo bicíclico puede contener de 8 a 12 átomos en el anillo. En una modalidad, uno o ambos grupos carbocíclicos del arilo bicíclico es independientemente se sustituye opcionalmente con uno o más de los siguientes grupos: -V-halógeno, -alquilo (C_1-C_6), -alquenilo (C_2-C_6), -alquinilo (C_2-C_6), - V-$N(R')_2$, metilenodioxo, etilenodioxo, -V-$NHSO_2R'$, -V-$NR'COR'$, -V-$NHCO_2R'$, -V-NO_2, -V-$SO_2N(R')_2$, -V-SO_2R', -V-OR', -V-COR', -V-CO_2R', -V-$CON(R')_2$, o -V-CN, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido, o arilo no sustituido; y en donde cada V es independientemente un enlace o alquilo (C_1-C_6).

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El término "arilo tricíclico" como se utiliza aquí se refiere a tres grupos carbocíclicos fusionados, en donde dos o tres de los grupos carbocíclicos es aromático. Por ejemplo, un arilo tricíclico puede contener de 13 a 18 átomos en el anillo. En una modalidad, uno o más de los grupos carbocíclicos del arilo tricíclico son independientemente se sustituye opcionalmente con uno o más de los siguientes grupos: -V-halógeno, -alquilo (C_1-C_6), -alquenilo (C_2-C_6), -alquinilo (C_2-C_6), - V-$N(R')_2$, metilenodioxo, etilenodioxo, -V-$NHSO_2R'$, -V-$NR'COR'$, - V-$NHCO_2R'$, -V-NO_2, -V-$SO_2N(R')_2$, -V-SO_2R', -V-OR', -V-COR', -V-CO_2R', -V-$CON(R')_2$, o -V-CN, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido, o arilo no sustituido; y en donde cada V es independientemente un enlace o alquilo (C_1-C_6).

El término "heteroarilo bicíclico" como se utiliza aquí se refiere a dos grupos cíclicos fusionados, en donde uno o ambos de los grupos cíclicos es aromático y contiene uno a cuatro heteroátomos seleccionados de O, S, y N. Por ejemplo, un heteroarilo bicíclico puede contener de 8 a 12 átomos en el anillo, y de 1 a 3 heteroátomos seleccionados de O, N, y S en cada anillo. En una modalidad, uno o ambos grupos cíclicos es independientemente se sustituye opcionalmente con uno o más de los siguientes grupos: -V-halógeno, -alquilo (C_1-C_6), -alquenilo (C_2-C_6), -alquinilo (C_2-C_6), -V-$N(R')_2$, metilenodioxo, etilenodioxo, -V-$NHSO_2R'$, -V-$NR'COR'$, -V-$NHCO_2R'$, -V-NO_2, -V-$SO_2N(R')_2$, -V-SO_2R', -V-OR', -V-COR', -V-CO_2R', -V-$CON(R')_2$, o -V-CN, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido, o

arilo no sustituido; y en donde cada V es independientemente un enlace o alquilo (C_1-C_6).

El término "heteroarilo tricíclico" como se utiliza aquí se refiere a tres grupos cíclicos fusionados, en donde dos o tres de los grupos cíclicos es aromático y por lo menos un grupo aromático contiene 1 a 4 heteroátomos seleccionados de O, S, y N. Por ejemplo, un arilo tricíclico puede contener de 13 a 18 átomos en el anillo, y de 1 a 3 heteroátomos seleccionados de O, N, y S en cada anillo. En una modalidad, los grupos cíclicos son independientemente sustituidos con uno o más de los siguientes grupos: -V-halógeno, -alquilo (C_1-C_6), -alquenilo (C_2-C_6), -alquinilo (C_2-C_6), -V-$N(R')_2$, metilenodioxo, etilenodioxo, -V-$NHSO_2R'$, -V-$NR'COR'$, -V-$NHCO_2R'$, -V-NO_2, -V-$SO_2N(R')_2$, -V-SO_2R', -V-OR', -V-COR', -V-CO_2R', -V-$CON(R')_2$, o -V-CN, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido, o arilo no sustituido; y en donde cada V es independientemente un enlace o alquilo (C_1-C_6).

Una porción opcionalmente sustituida se puede sustituir con uno o más sustituyentes, ejemplos de los cuales son como se ilustran aquí. En una modalidad, una porción "opcionalmente sustituida" se sustituye con uno o más de los siguientes: -V- halógeno, -alquilo (C_1-C_6), -alquenilo (C_2-C_6), -alquinilo (C_2-C_6), -V-$N(R')_2$, metilenodioxo, etilenodioxo, -V-$NHSO_2R'$, -V-$NR'COR'$, -V-$NHCO_2R'$, -V-NO_2, -V-$SO_2N(R')_2$, -V-SO_2R', -V-OR', -V-COR', -V-CO_2R', -V-$CON(R')_2$, o -V-CN, en donde cada R' es independientemente hidrógeno, alquilo (C_1-C_6) no sustituido, o

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arilo no sustituido; y en donde cada V es independientemente un enlace o alquilo (C_1-C_6).

Cuando tales porciones se sustituyen, por ejemplo, ellas típicamente pueden ser mono-, di-, tri- o persustituidas. Ejemplos para un sustituyente halógeno incluyen 1-bromo vinilo, 1-fluoro vinilo, 1,2-difluoro vinilo, 2,2-difluorovinilo, 1,2,2-trifluoro vinilo, 1,2- dibromo etano, 1,2 difluoro etano, 1-fluoro-2-bromo etano, CF_2F_3, $CF_2CF_2CF_3$, y similares.

El término halógeno incluye bromo, cloro, flúor, y yodo.

Por simplicidad, no se representan los puntos de conexión ("-"). Cuando un átomo o compuesto se describe para definir una variable, se entiende que este está previsto para reemplazar la variable en una forma para satisfacer la valencia del átomo o compuesto. Por ejemplo, si "X*" es C(R*)=C(R*), ambos átomos de carbono forman una parte del anillo con el fin de satisfacer sus valencias respectivas. En forma similar, cuando los sustituyentes divalentes están presentes, se entiende que ellos no se limitan al orden listado, por ejemplo, como se utiliza en esta especificación "OCH_2" abarca CH_2O y OCH_2.

El término "administrar", "que administra", o "administración", como se utiliza aquí se refiere a administrar directamente un compuesto o sal farmacéuticamente aceptable del compuesto o una composición a un animal, o

administrar un derivado de prodroga o análogo del compuesto o sal farmacéuticamente aceptable del compuesto o composición al animal, que puede formar una cantidad equivalente del compuesto activo dentro del cuerpo del animal.

El término "animal" como se utiliza aquí incluye, sin limitación, un humano, ratón, rata, conejillo de Indias, perro, gato, caballo, vaca, cerdo, mono, chimpancé, babuino, o macaco. En una modalidad, el animal es un mamífero. En otra modalidad, el animal es u humano.

El término "grupo protector amina" como se utiliza aquí se refiere a una porción que bloquea temporalmente un sitio amina reactivo en un compuesto. Generalmente, esto se hace para que una reacción química se pueda llevar a cabo en otro sitio reactivo en un compuesto multifuncional o de otra forma estabiliza la amina. En una modalidad, un grupo protector amina se remueve selectivamente mediante una reacción química. Un grupo protector amina de ejemplo es un grupo protector 9-fluorenilmetoxicarbonilo. Otro grupo protector amina de eje es un grupo protector carbamato. Grupos protectores carbamato incluyen, sin limitación, t-butil carbamato, metil carbamato, etil carbamato, 2,2,2-tricloroetil carbamato, 2-(trimetilsilil)etil carbamato, 1,1-dimetil-2,2,2-tricloroetil carbamato, bencil carbamato, p-metoxibencil carbamato, p-nitrobencilcarbamato, p-bromobencil carbamato, p-clorobencil carbamato, y 2,4-diclorobencil carbamato. Ver, Greene and Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, John Wiley & Sons (1991).

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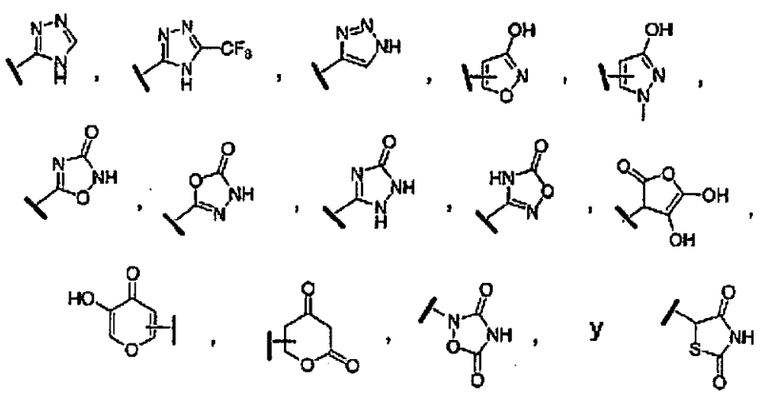
El término "grupo protector de ácido carboxílico" como se utiliza aquí se refiere a una porción que bloquea temporalmente un sitio reactivo de ácido carboxílico en un compuesto. Generalmente, esto se hace de tal manera que una reacción química se pueda llevar a cabo en otro sitio reactivo en un compuesto multifuncional o estabiliza de otra forma el ácido carboxílico. En una modalidad, a grupo protector de ácido carboxílico se remueve selectivamente mediante una reacción química. Un grupo protector de ácido carboxílico de ejemplo es un grupo protector de éster de alquilo, tal como un terc-butil éster.

El término "grupo de ácido mimético" como se utiliza aquí se refiere a una porción que tiene similitudes químicas y físicas que producen propiedades biológicas ampliamente similares a un ácido. En una modalidad, un grupo de ácido mimético es un heterociclo de 5 o 6-miembros que contiene 1 a 4 heteroátomos seleccionados de O, N, S. Grupos de ñacido miméticos de ejemplo incluyen:



El término "condiciones efectivas para" como se utiliza aquí se refiere a condiciones de reacción sintéticas que serán evidentes para aquellos expertos en la técnica de química orgánica sintética.

El término "cantidad efectiva" como se utiliza aquí se refiere a una cantidad de un compuesto o sal farmacéuticamente aceptable de un compuesto que, cuando se administra a un animal, es efectiva para prevenir, para por lo menos mejorar parcialmente, o para curar, una condición de la que el animal sufre o se sospecha que sufre.

El término "trastorno relacionado con metaloproteinasa" se utiliza aquí se refiere a una afección para la que sería benéfico modular la actividad de la metaloproteinasa. Trastornos relacionado con metaloproteinasas de ejemplo incluyen, sin limitación, trastornos artríticos, osteoartritis, cáncer, artritis reumatoide, asma, enfermedad pulmonar obstructiva crónica, aterosclerosis, degeneración macular relacionada con la edad, infarto de miocardio, ulceración de córnea y otras enfermedades de superficie ocular, hepatitis, aneurismas aórticos, tendonitis, enfermedades del sistema nervioso central, cicatrización de heridas anormal, angiogénesis, reestenosis, cirrosis, esclerosis múltiple, glomerulonefritis, enfermedad del anfitrión versus injerto, diabetes, enfermedad inflamatoria del intestino, choque, degeneración de disco intervertebral, apoplejía, osteopenia, y enfermedades periodontales.

El término "modulador de metaloproteinasa" se refiere a un compuesto que es capaz de modular la expresión de una metaloproitenasa. Por ejemplo, un modulador de metaloproteinasa puede mejorar la expresión metaloproteinasa. Un modulador de metaloproteinasa también puede ser un inhibidor de una metaloproitenasa.

El término "aislado y purificado" como se utiliza aquí se refiere a un aislado que se separa de otros componentes de una mezcla de reacción o una fuente natural. En ciertas modalidades, el aislado contiene por lo menos aproximadamente 50%, por lo menos aproximadamente 55%, por lo menos aproximadamente 60%, por lo menos aproximadamente 65%, por lo menos aproximadamente 70%, por lo menos aproximadamente 75%, por lo menos aproximadamente 80%, por lo menos aproximadamente 85%, por lo menos aproximadamente 90%, por lo menos aproximadamente 95%, o por lo menos aproximadamente 98% del compuesto o sal farmacéuticamente aceptable del compuesto en peso del aislado.

Como se utiliza aquí, un compuesto de la invención incluye una sal farmacéuticamente aceptable de este. El término "sal farmacéuticamente aceptable" como se utiliza aquí se refiere a una sal de un ácido y un átomo de nitrógeno básico de un compuesto de la presente invención. Sales de ejemplo incluyen, pero no se limitan a, sulfato, citrato, acetato, oxalato, cloruro, clorhidrato, bromuro, bromohidrato, yoduro, nitrato, bisulfato, fosfato, fosfato ácido, isonicotinato, lactato, salicilato, citrato ácido, tartrato, oleato, tanato,

pantotenato, bitartrato, ascorbato, succinato, maleato, gentisinato, fumarato, gluconato, glucaronato, sacarato, formato, benzoato, glutamato, metanosulfonato, etanosulfonato, bencenosulfonato, p-toluenosulfonato, canforsulfonato, naftalenosulfonato, propionato, succinato, fumarato, maleato, malonato, mandelato, malato, ftalato, y pamoato. El término "sal farmacéuticamente aceptable" como se utiliza aquí también se refiere a una sal de un compuesto de la presente invención que tiene un grupo funcional acídico, tal como un grupo funcional ácido carboxílico, y una base. Bases de ejemplo incluyen, pero no se limitan a, hidróxido de metales álcali que incluyen sodio, potasio, y litio; hidróxidos de metales alcalinotérreos tal como calcio y magnesio; hidróxidos de otros metales, tal como aluminio y zinc; amoniaco, aminas orgánicas tal como mono-, di-, o tri-alquilaminas sustituidas con hidroxilo o no sustituidas, diciclohexilamina; tributil amina; piridina; N-metilo, N-etilamina; dietilamina; trietilamina; mono-, bis-, o tris-(2-OH-alquilamina (C_1-C_6)), tal como N,N-dimetil-N-(2-hidroxietil)amina o tri-(2-hidroxietil)amina; N-metil-D-glucamina; morfolina; tiomorfolina; piperidina; pirrolidina; y aminoácidos tales como arginina, lisina, y similares. El término "sal farmacéuticamente aceptable" también incluye un hidrato de un compuesto de la presente invención.

El término "sustancialmente libre de su enantiómero opuesto correspondiente" como se utiliza aquí significa que el compuesto contiene no más de aproximadamente 10% en peso de su enantiómero opuesto correspondiente. En otras modalidades,

el compuesto que es sustancialmente libre de su enantiómero opuesto correspondiente contiene no más de aproximadamente 5%, no más de aproximadamente 1%, no más de aproximadamente 0.5%, o no más de aproximadamente 0.1% en peso de su enantiómero opuesto correspondiente. Un enantiómero que es sustancialmente libre de su enantiómero opuesto correspondiente incluye un compuesto que se ha aislado y purificado o se ha preparado sustancialmente libre de su enantiómero opuesto correspondiente. El término "tautómero" como se utiliza aquí se refiere a compuestos producidos por el fenómeno en donde un protón de un átomo de una molécula cambia a otro átomo. *Ver*, Jerry March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, Fourth Edition, John Wiley & Sons, páginas 69-74 (1992).

Las siguientes abreviaturas como se utiliza aquí significan: Ac es acetato; boc es t- butil carbamato; Bu es butilo; DIEA es diisopropiletilamina; DMF es dimetilformamida; DMSO es dimetilsulfóxido; ESI es ionización por electrorociado; Et es etilo; HPLC es cromatografía líquida de alta presión; HRMS es espectrometría de masa de alta resolución; Me es metilo; MS es espectrometría de masa; *m/z* es proporción de carga a masa; t.r. es tiempo de retención; TFA es ácido trifluoroacético; THF es tetrahidrofurano; FMOC es 9-fluorenilmetoxicarbonilo; DEA es dietilamina; DME es dimetoxietano; Bop es hexafluorofosfato de benzotriazol-1-il-oxi-tris-(dimetilamino)-fosfonio; PyBop es hexafluorofosfato de benzotriazol-1-il-oxi-tris-pirrolidino-fosfonio; HBTU es O-benzotriazol-N,N,N',N'-tetrametil-uronium-hexafluoro-fosfato;

y EDC es clorhidrato de 1-(3-dimetilaminopropil)-3-etil-carbodiimida.

Compuestos y Sales Farmacéuticamente Aceptables de Compuestos de la Invención

Los compuestos o sales farmacéuticamente aceptables de compuestos de la presente invención pueden contener un átomo de carbono asimétrico y algunos de los compuestos o sales farmacéuticamente aceptables de compuestos de la invención pueden contener uno o más centros asimétricos, y puede así dar lugar a isómeros ópticos y diastereómeros. Mientras se describen independientes a la estereoquímica en los compuestos o sales farmacéuticamente aceptables de compuestos de la presente invención, la presente invención incluye tales isómeros ópticos y diastereómeros, así también como estereoisómeros R y S enantioméricamente puros, resueltos y racémicos, y también otras mezclas de los estereoisómeros R y S y sales farmacéuticamente aceptables de estos. En donde se proporciona un estereoisómero, este puede en algunas modalidades ser suministrado sustancialmente libre de su enantiómero opuesto correspondiente.

Adicionalmente, los compuestos y sales farmacéuticamente aceptables de compuestos de la presente invención pueden existir como tautómeros. Dichos tautómeros pueden ser transitorias o aislables como un producto estable. Estos tautómeros están dentro del alcance de la presente invención.

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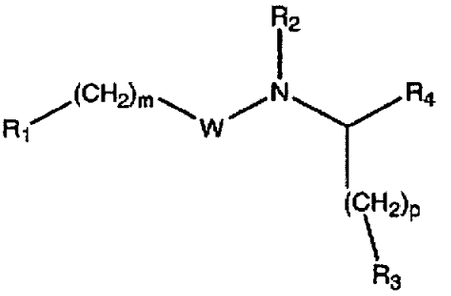
Prodrogas de los compuestos o sales farmacéuticamente aceptables de compuestos también están dentro del alcance de la presente invención.

Compuestos de la Fórmula (I)

En una modalidad, la presente invención se dirige a compuestos de la Fórmula (I):



(I)

y sales farmacéuticamente aceptables de estos, en donde

W es -C(O)-, -OC(O)-, -NHC(O)-, -C(O)O-, o -C(O)NH-;

R_1 es fenilo, heteroarilo, bifenilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada uno se sustituye opcionalmente con uno o más de R_5 o R_6, y cuando R_1 se sustituye con más de uno de R_5 o R_6, los sustituyentes pueden ser idénticos o diferentes;

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), -$(CH_2)_nR_{11}$, -OH, o -O-alquilo (C_1-C_6);

R_3 es $-CO_2H$, $-CONH_2$, -CONHOH, $-CONHSO_2R_7$, tetrazol, $-SO_2NHR_7$, $-SO_3H$, $-PO(OH)NH_2$, $-PO(OH)OR_7$, $-CONHR_7$, $-COOR_7$, un grupo de ácido mimético, o un heterocicloalquilo de 5 o 6 miembros o heteroarilo que contiene 1 a 4 heteroátomos seleccionados de O, N, S;

R_4 es $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, o $-CONR_9R_{10}$;

R_5 es arilo, heteroarilo, $-(CH_2)_n$-arilo, $-(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S- arilo, -S-heteroarilo, -NH-arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO- arilo, -CO-heteroarilo, $-SO_2$-alquilo (C_1-C_6), $-SO_2$-arilo, $-SO_2$-heteroarilo, $-SO_2NH$-arilo, $-SO_2NH$-heteroarilo, $-NHSO_2$-alquilo (C_1-C_6), $-NHSO_2$-arilo, $-NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R_5 se sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes;

R_6 y R_{12} son cada uno independientemente hidrógeno, halógeno, -CN, $-OCF_3$, $-CF_3$, $-NO_2$, -OH, -SH, $-NR_7R_8$, $-CONR_7R_8$, $-NR_8COR_7$, $-NR_8CO_2R_7$, $-CO_2R_7$, $-COR_7$, $-SO_2$-alquilo (C_1-C_6), $-SO_2$-arilo, $-SO_2$-heteroarilo, $-SO_2R_7$, $-NR_7SO_2R_8$, $-SO_2NR_7R_8$;

alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, -$(CH_2)_n$-arilo, o -$(CH_2)_n$-heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_9 y R_{10} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), alquilo (C_1-C_6)-OH, alquilo (C_1-C_6)-O-alquilo (C_1-C_6), arilo, cicloalquilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más R_{12};

o R_9 y R_{10} juntos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_{11} es arilo, heteroarilo, o cicloalquilo;

R_{13} es halógeno, -O-alquilo (C_1-C_6), $-CO_2H$, -OH, $-CF_3$, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con $-NH_2$, arilo sustituido con -O- alquilo (C_1-C_6), $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo;

m es 0-4;

n es 0-4; y

p es 0-2.

En una modalidad, W es -CO.

En otra modalidad, R_3 es $-CO_2H$.

En una modalidad, R_1 es arilo bicíclico opcionalmente sustituido con uno o más de R_5 y R_6.

En otra modalidad, R_1 es arilo tricíclico opcionalmente sustituido con uno o más de R_5 y R_6.

En una modalidad, R_1 es bifenilo opcionalmente sustituido con uno o más de R_5 y R_6.

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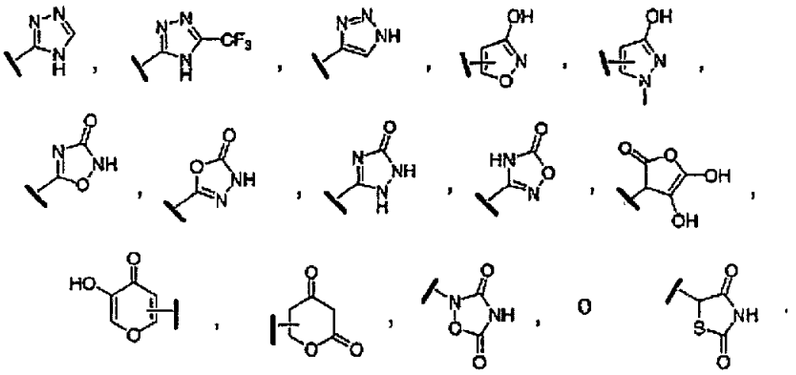
En una modalidad, m es 0-2. En otra modalidad, m es 0.

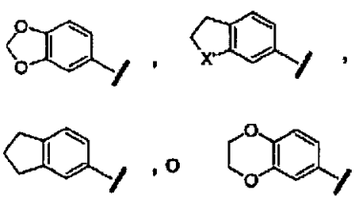
En una modalidad, p es 0-2. En otra modalidad, p es 2.

En otra modalidad, m es 0 y p es 2.

En otra modalidad, R_3 es



En otra modalidad, R_5 es



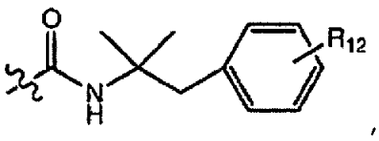
en donde X' es O, S, o NH.

En una modalidad, R_4 es $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, o $-CONR_9R_{10}$.

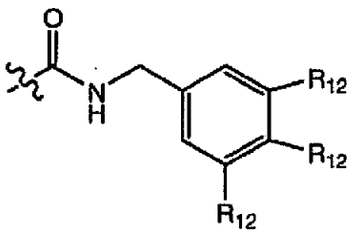
En una modalidad, W es -CO, R_2 es hidrógeno, R_3 es $-CO_2H$, R_1 es bifenilo opcionalmente sustituido con uno o más de R_5 y R_6, R_4 es $-CONR_9R_{10}$, m es 0, y p es 2.

En otra modalidad, cuando R_4 es diferente de hidrógeno, el compuesto o sal farmacéuticamente aceptable del compuesto es el S-enantiómero con respecto al carbono al cual R_4 se une.

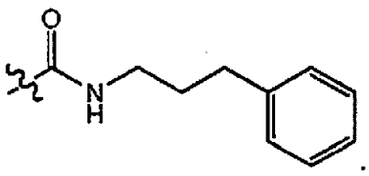
En una modalidad, R_2 es hidrógeno,

R_4 es  , y cada R_{12} es $-OCH_3$.

En una modalidad, R_2 es hidrógeno,

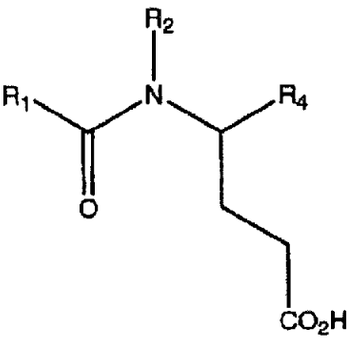
R_4 es  , y cada R_{12} es $-OCH_3$.

En otra modalidad, R_2 es hidrógeno; y

R_4 es  .

Compuestos de la Fórmula (Ia)

En una modalidad, la invención se dirige a compuestos de la Fórmula (Ia):



(Ia)

y sales farmacéuticamente aceptables de estos, en donde

R_1 es fenilo, heteroarilo, bifenilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada uno se sustituye opcionalmente con uno o más de R_5 o R_6, y cuando R_1 se sustituye con más de uno de R_5 o R_6, los sustituyentes pueden ser idénticos o diferentes;

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), -$(CH_2)_nR_n$, -OH, o -O-alquilo (C_1-C_6);

R_4 es -CO_2H, -$CONH_2$, -$(CH_2)_nOR_7$, o -$CONR_9R_{10}$;

R_5 es arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S- arilo, -S-heteroarilo, -NH-arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO-arilo, -CO-heteroarilo, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2NH-arilo, -SO_2NH-heteroarilo, -$NHSO_2$-alquilo (C_1-C_6), -$NHSO_2$-arilo, -$NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-

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alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R_5 se sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes;

R_6 y R_{12} son cada uno independientemente hidrógeno, halógeno, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo

(C_2-C_6), cicloalquilo, $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_9 y R_{10} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), alquilo (C_1-C_6)-OH, alquilo (C_1-C_6)-O-alquilo (C_1-C_6), arilo, cicloalquilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más R_{12}; o R_9 y R_{10} juntos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_{11} es arilo, heteroarilo, o cicloalquilo;

R_{13} es halógeno, -O-alquilo (C_1-C_6), $-CO_2H$, -OH, $-CF_3$, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con $-NH_2$, arilo sustituido con -O-alquilo (C_1-C_6), $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo; y n es 0-4.

En una modalidad, R_1 es arilo bicíclico opcionalmente sustituido con uno o más de R_5 y R_6.

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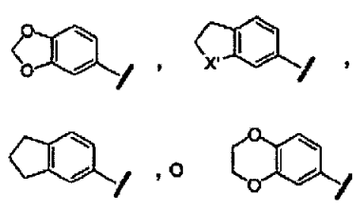
En otra modalidad, R_1 es arilo tricíclico opcionalmente sustituido con uno o más de R_5 y R_6.

En una modalidad, R_1 es bifenilo opcionalmente sustituido con uno o más de R_5 y R_6.

En una modalidad, R_4 es $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, o $-CONR_9R_{10}$.

En una modalidad, R_1 es bifenilo opcionalmente sustituido con uno o más de R_5 y R_6, y R_4 es $-CONR_9R_{10}$.

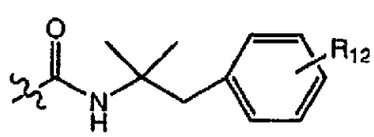
En otra modalidad, R_5 es



en donde X' es O, S, o NH.

En otra modalidad, cuando R_4 es diferente de hidrógeno, el compuesto o sal farmacéuticamente aceptable del compuesto es el S-enantiómero con respecto al carbono al cual R_4 se une.

En una modalidad, R_2 es hidrógeno,

R_4 es  , y R_{12} es -F.

En una modalidad, R_2 es hidrógeno,

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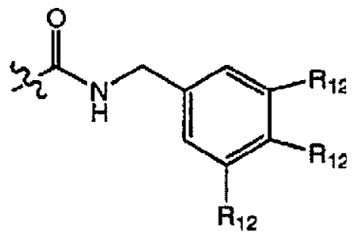
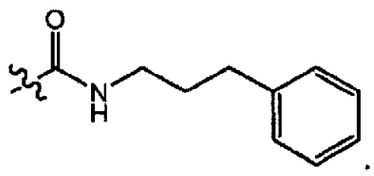
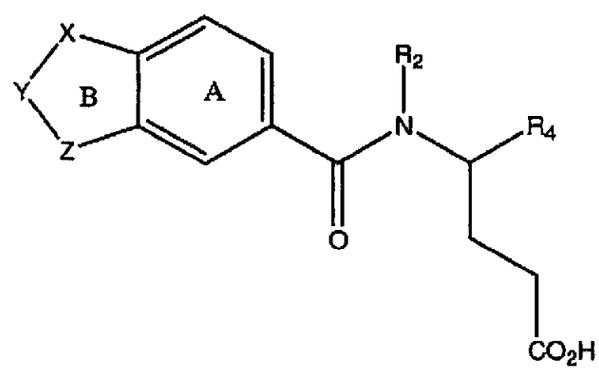
R_4 es  , y R_{12} es $-OCH_3$.

En otra modalidad, R_2 es hidrógeno; y

R_4 es  .

Compuestos de la Fórmula (Ib)

En una modalidad, la invención se dirige a compuestos de la Fórmula (Ib):



(Ib)

y sales farmacéuticamente aceptables de estos, en donde

X, Y, y Z son cada uno independientemente $(CH_2)_n$, O, S, NR_7, CO, o SO_2; o X, Y, y Z forman un benceno en el anillo B; el anillo A y el anillo B son cada uno independientemente opcionalmente sustituidos con uno o más de R_5 y R_6;

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), -$(CH_2)_nR_{11}$, -OH, o -O-alquilo (C_1-C_6);

R_4 es -CO_2H, -$CONH_2$, -$(CH_2)_nOR_7$, o -$CONR_9R_{10}$;

R_5 es arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, -S-heteroarilo, -NH-arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO-arilo, -CO-heteroarilo, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2NH-arilo, -SO_2NH-heteroarilo, -$NHSO_2$-alquilo (C_1-C_6), -$NHSO_2$-arilo, -$NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R_5 se sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes;

R_6 y R_{12} son cada uno independientemente hidrógeno, halógeno, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo

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(C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S- arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, -$(CH_2)_n$-arilo, o -$(CH_2)_n$- heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_9 y R_{10} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), alquilo (C_1-C_6)-OH, alquilo (C_1-C_6)-O-alquilo (C_1-C_6), arilo, cicloalquilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más R_{12}; o R_9 y R_{10} juntos pueden formar un grupo cíclico de

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cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_{11} es arilo, heteroarilo, o cicloalquilo;

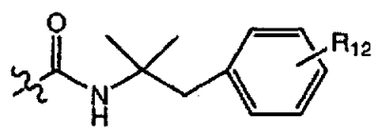
R_{13} es halógeno, -O-alquilo (C_1-C_6), $-CO_2H$, -OH, $-CF_3$, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con $-NH_2$, arilo sustituido con -O- alquilo (C_1-C_6), $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo; y

n es 0-4.

En una modalidad, R_4 es $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, o $-CONR_9R_{10}$.

En otra modalidad, cuando R_4 es diferente de hidrógeno, el compuesto o sal farmacéuticamente aceptable del compuesto es el S-enantiómero con respecto al carbono al cual R_4 se une.

En una modalidad, R_2 es hidrógeno,

R_4 es  , y R_{12} es -F.

En una modalidad, R_2 es hidrógeno,

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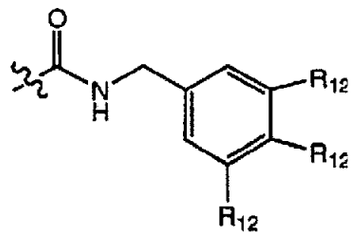
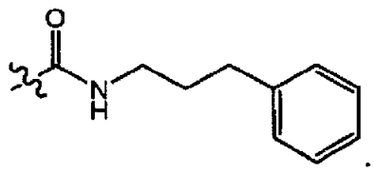
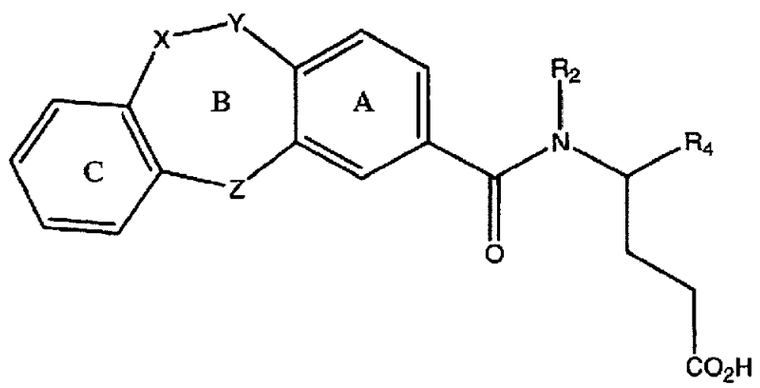
R_4 es  , y R_{12} es $-OCH_3$.

En otra modalidad, R_2 es hidrógeno; y

R_4 es  .

Compuestos de la Fórmula (Ic)

En una modalidad, la invención se dirige a compuestos de la Fórmula (Ic):



(Ic)

y sales farmacéuticamente aceptables de estos,

en donde

X, Y, y Z son cada uno independientemente $(CH_2)_n$, O, S, NR_7, CO, o SO_2; o X, Y, y Z forman un benceno en el anillo B; ek anillo A, el anillo B, y el anillo C son cada uno

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independientemente sustituidos opcionalmente con uno o más de R_5 y R_6;

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), $-(CH_2)_nR_{11}$, -OH, o -O-alquilo (C_1-C_6);

R_4 es $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, o $-CONR_9R_{10}$;

R_5 es arilo, heteroarilo, $-(CH_2)_n$-arilo, $-(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S- arilo, -S-heteroarilo, -NH-arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO- arilo, -CO-heteroarilo, $-SO_2$-alquilo (C_1-C_6), $-SO_2$-arilo, $-SO_2$-heteroarilo, $-SO_2NH$-arilo, $-SO_2NH$-heteroarilo, $-NHSO_2$-alquilo (C_1-C_6), $-NHSO_2$-arilo, $-NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH- alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R_5 se sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes;

R_6 y R_{12} son cada uno independientemente hidrógeno, halógeno, -CN, $-OCF_3$, $-CF_3$, $-NO_2$, -OH, -SH, $-NR_7R_8$, $-CONR_7R_8$, $-NR_8COR_7$, $-NR_8CO_2R_7$, $-CO_2R_7$, $-COR_7$, $-SO_2$-alquilo (C_1-C_6), $-SO_2$-arilo, $-SO_2$-heteroarilo, $-SO_2R_7$, $-NR_7SO_2R_8$, $-SO_2NR_7R_8$;

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alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S- arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, -$(CH_2)_n$-arilo, o -$(CH_2)_n$-heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_9 y R_{10} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), alquilo (C_1-C_6)-OH, alquilo (C_1-C_6)-O-alquilo (C_1-C_6), arilo, cicloalquilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más R_{12};

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o R_9 y R_{10} juntos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_{11} es arilo, heteroarilo, o cicloalquilo;

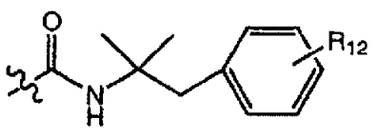
R_{13} es halógeno, -O-alquilo (C_1-C_6), $-CO_2H$, -OH, $-CF_3$, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con $-NH_2$, arilo sustituido con -O- alquilo (C_1-C_6), $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo; y

n es 0-4.

En una modalidad, R_4 es $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, o $-CONR_9R_{10}$.

En otra modalidad, cuando R_4 es diferente de hidrógeno, el compuesto o sal farmacéuticamente aceptable del compuesto es el S-enantiómero con respecto al carbono al cual R_4 se une.

En una modalidad, R_2 es hidrógeno,

R_4 es  , y R_{12} es -F.

En una modalidad, R_2 es hidrógeno,

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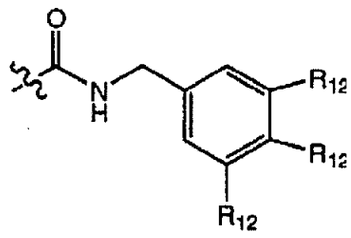
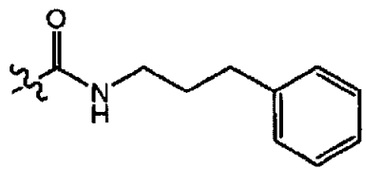
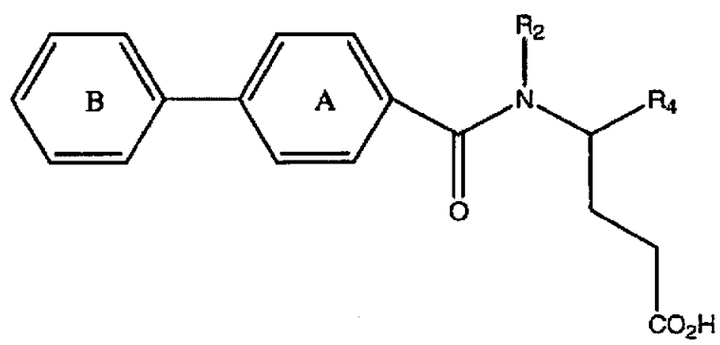
R_4 es  , y R_{12} es $-OCH_3$.

En otra modalidad, R_2 es hidrógeno; y

R_4 es  .

Compuestos de la Fórmula (Id)

En una modalidad, la invención se dirige a compuestos de la Fórmula (Id):



(Id)

y sales farmacéuticamente aceptables de estos,

en donde

el anillo A y el anillo B son cada uno independientemente sustituidos opcionalmente con uno o más de R_5 y R_6;

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R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), -$(CH_2)_nR_{11}$, -OH, o -O-alquilo (C_1-C_6);

R_4 es -CO_2H, -$CONH_2$, -$(CH_2)_nOR_7$, o -$CONR_9R_{10}$;

R_5 es arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S- arilo, -S-heteroarilo, -NH-arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO-arilo, -CO-heteroarilo, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2NH-arilo, -SO_2NH-heteroarilo, -$NHSO_2$-alquilo (C_1-C_6), -$NHSO_2$-arilo, -$NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH- alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R5 se sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes;

R_6 y R_{12} son cada uno independientemente hidrógeno, halógeno, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6),

-NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo, $-(CH_2)_n$-arilo, $-(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_9 y R_{10} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), alquilo (C_1-C_6)-OH, alquilo (C_1-C_6)-O-alquilo (C_1-C_6), arilo, cicloalquilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más R_{12}; o R_9 y R_{10} juntos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

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R_{11} es arilo, heteroarilo, o cicloalquilo;

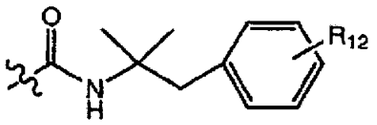
R_{13} es halógeno, -O-alquilo (C_1-C_6), $-CO_2H$, -OH, $-CF_3$, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con $-NH_2$, arilo sustituido con -O- alquilo (C_1-C_6), $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo; y

n es 0-4.

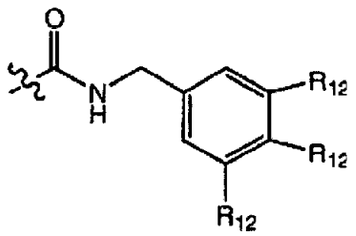
En una modalidad, R_4 es $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, o $-CONR_9R_{10}$.

En otra modalidad, cuando R_4 es diferente de hidrógeno, el compuesto o sal farmacéuticamente aceptable del compuesto es el S-enantiómero con respecto al carbono al cual R_4 se une.

En una modalidad, R_2 es hidrógeno,

R_4 es  , y R_{12} es -F.

En una modalidad, R_2 es hidrógeno,

R_4 es  , y R_{12} es $-OCH_3$.

En otra modalidad, R_2 es hidrógeno; y

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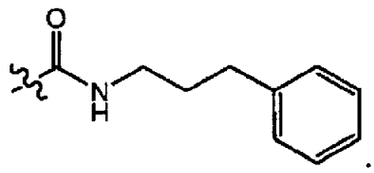
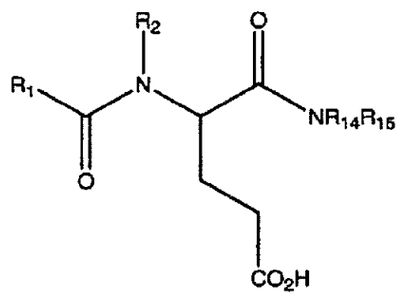
R_4 es  .

Compuestos de la Fórmula (II)

En otra modalidad, la invención proporciona compuestos de la Fórmula (II):



(II)

y sales farmacéuticamente aceptables de estos, en donde

R_1 es fenilo, alquilo (C_1-C_6) sustituido con fenilo, heteroarilo, bifenilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada uno se sustituye opcionalmente con uno o más de R_5 o R_6, y cuando R_1 se sustituye con más de uno de R_5 o R_6, los sustituyentes pueden ser idénticos o diferentes;

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), $-(CH_2)_pR_{11}$, -OH, o -O-alquilo (C_1-C_6);

R_5 es arilo, heteroarilo, $-(CH_2)_n$-arilo, $-(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, -S-heteroarilo, -NH-

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arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO- arilo, -CO-heteroarilo, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2NH-arilo, -SO_2NH-heteroarilo, -$NHSO_2$-alquilo (C_1-C_6), -$NHSO_2$-arilo, -$NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH- alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R_5 se sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes;

R_6 y R_{12} son cada uno independientemente hidrógeno, halógeno, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S- arilo, o -S-heteroarilo; cada alquilo,

arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, -$(CH_2)_n$-arilo, o -$(CH_2)_n$-heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_{11} es arilo, heteroarilo, o cicloalquilo;

R_{13} es halógeno, -O-alquilo (C_1-C_6), -CO_2H, -OH, -CF_3, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con -NH_2, arilo sustituido con -O- alquilo (C_1-C_6), -$(CH_2)_n$-arilo, o -$(CH_2)_n$-heteroarilo;

R_{14} y R_{15} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, heterocicloalquilo -$(CH_2)_n$- arilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más R_{12}; o R_{14} y R_{15} juntos pueden formar un grupo cíclico de cinco- a siete-

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miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

n es 0-4, y

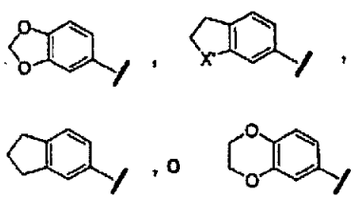
p es 0-2.

En una modalidad, R_1 es arilo bicíclico opcionalmente sustituido con uno o más de R_5 y R_6.

En otra modalidad, R_1 es arilo tricíclico opcionalmente sustituido con uno o más de R_5 y R_6.

En una modalidad, R_1 es bifenilo opcionalmente sustituido con uno o más de R_5 y R_6.

En otra modalidad, R_5 es



en donde X' es O, S, o NH.

En otra modalidad, R_2 es hidrógeno.

En una modalidad, el compuesto de Fórmula (I) es N^2-(4-benzoilbenzoil)-N^1-bencil-L-α-glutamina, ácido N-(4-benzoilbenzoil)-L-glutámico, N^1-(1,3-benzodioxol-5-ilmetil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-butil-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclopropil-L-α-glutamina, N^2-(1,1'-

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bifenil-4-ilcarbonil)-N^1-ciclohexil-L-α-glutamina; N^1-bencil-N^2-(4-tien-2-ilbenzoil)-L-α-glutamina, N^1-bencil-N^2-[4-(2-furil)benzoil]-L-α-glutamina, N^1-bencil-N^2-[(4'-etinil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fluorobencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclooctil-L-α-glutamina, N^1-bencil-N^2-(4-bromobenzoil)-L-α-glutamina, N^1-bencil-N^2-[(2',5'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-dimetoxibencil)-L-α-glutamina, N^1-bencil-N^2-(4-piridin-4-ilbenzoil)-L-α-glutamina, N^1-bencil-N^2-[(3'-5'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^1-bencil-N^2-[(4'-etil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^1-bencil-N^2-[(3'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^1-bencil-N^2-[(2'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^1-bencil-N^2-[(2',6'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclopentil-L-α-glutamina, N^1-[2-(acetilamino)etil]-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina, N^1-2-adamantil-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina, N^1-(2-adamantilmetil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina, N^1-bencil-N^2-(4-piridin-2-ilbenzoil)-L-α-glutamina, N^1-bencil-N^2-(4-piridin-3-ilbenzoil)-L-α-glutamina, N^1-bencil-N^2-[4-(1,3-tiazol-2-il)benzoil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metoxibencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3,4-dimetoxifenil)etil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metoxietil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(4-metoxifenil)etil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(1-naftilmetil)-

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L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-metilbencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-furilmetil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-metoxibencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,4-diclorobencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-(trifluorometoxi)bencil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[3-(trifluorometoxi)bencil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-(metiltio)bencil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fenoxibencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3-metoxifenil)etil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,4-dimetoxibencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metoxibencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-diclorobencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,5-difluorobencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^5-hidroxi-N^1[3-(trifluorometoxi)bencil]-1-glutamamida, N^2-(1,1'-bifenil-4-ilcarbonil)-N^5-hidroxi-N^1-[2-(3-metoxifenil)etil]-1-glutamamida, N^2-(1,1'-bifenil-4-ilcarbonil)-N^5-hidroxi-N^1-(3,4,5-trimemoxibenzil)-L-glutamamida, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,5-dimetoxibencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,5- dimetoxibencil)-N^5-hidroxi-L-glutamamida, N^1-bencil-N^2-[(4'-vinil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-dimetilbencil)-L-α-glutamina,, N^1-bencil-N^2-[(4'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^1-bencil-N^2-[(4'-

propoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^1-bencil-N^2-[(4'-butoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^1-bencil-N^2-{[4'-(ciclobutilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina, N^1-bencil-N^2-{[4'-(ciclohexilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina, N^2-{[4'-(aliloxi)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N1-(3,4-dimetilbencil)-N^5-hidroxi-L-glutamamida, N^2-(1,1'-bifenil-4-ilacetil)-N^1-(3-metoxibencil)-L-α-glutamina, N^2-[(3-fluorofenil)acetill-N^1-(3-metoxibencil)-L-α-glutamina, N^2-{[4'-(acetilamino)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutamina, N^1-bencil-N^2-{[4'-(2-furoilamino)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina, N^1-bencil-N^2-({4'-[(4-fluorobenzoil)amino]-1,1'-bifenil-4-il}carbonil)-L-α-glutamina, N^2-{[4'-(benzoilamino)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutamina, N^1-bencil-N^2-(5-fenil-2-furoil)-L-α-glutamina, N^1-bencil-N^2-[5-(3,5-etoxifenil)-2-furoil]-L-α-glutamina, N^1-bencil-N^2-[5-(3,5-dimetilfenil)-2-furoil]-L-α-glutamina, N^1-bencil-N^2-(2,2'-bifuran-5-ilcarbonil)-L-α-glutamina, N^1-bencil-N^2-(5-tien-2-il-2-furoil)-L-α-glutamina, N^2-[(2,2'-dimetil-1,1'-bifenil-4-il)carbonil]-N^1-(3-metoxibencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-feniletil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[3-(trifluorometil)bencil]-L-α-glutamina, N^1-(4-aminobencil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina, N^1-(3-aminobencil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(trifluorometil)bencil]-L-α-glutamina, N^1-bencil-N^2-[(2-fluoro-1,1'-bifenil-4-il)carbonil]-L-α-

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glutamina, N^2-(-1,1'-bifenil-4-ilcarbonil)-N^1-(3-fluorobencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutamina, N^1-bencil-N^2-(1,1'-bifenil-3-ilcarbonil)-L-α-glutamina, N^1-bencil-N^2-(3-tien-2-ilbenzoil)-L-α-glutamina, N^1-bencil-N^2-[(3-cloro1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^1-bencil-N^2-[(3-fluoro-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^1-bencil-N^2-[(2,6-dimetoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3-clorofenil)etil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-fluorobencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-difluorobencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metilbencil)-L-α-glutamina, N^1-bencil-N^2-({4'-[(3-metoxibencil)oxi]-1,1'-bifenil-4-il}carbonil)-L-α-glutamina, N^1-*bencil*-N^2-({4'-[(3,5-dimetoxibencil)oxi]-1,1'-bifenil-4-il}carbonil)-L-α-glutamina, N^1-bencil-N^2-{[4'-(2-naftilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-2,3-dihidro-1*H*-inden-2-il-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,3-dimetilbencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fenilbutil)-L-α-glutamina, N^1-(2-bencilfenil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metoxi-1,1'-bifenil-3-il)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metilbencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-fluoro-3-(trifluorometil)bencil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-heptil-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-yodobencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-vinilbencil)-L-α-glutamina, N^2-(1,1'-

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bifenil-4-ilcarbonil)-N^1-(3-tien-2-ilbencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, N^1-bencil-N^2-[(6-fenilpiridin-3-il)carbonill-L-α-glutamina, N^1-(3-metoxibencil)-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-*terc*-butilbencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-yodobencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-vinilbencil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(sec-butil)-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(ciclopropilmetil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[4-(dimetilamino)bencil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-bromofenil)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(2-bifenil-4-iletil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2'-etoxibifenil-4-il)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-etinilbifenil-4-il)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4-(2-tienil)fenil]etil}-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-piridin-2-ilfenil)etil]-L-α-glutamina, N^2-bifenil-4-ilcarbonil)-N^1-[3-(dimetilamino)bencil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(3,3-difenilpropil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(3,3-dimetilbutil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-isopropil-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(piridin-4-ilmetil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1,N^1-dietil-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(1,1-dimetilpropil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-4-il)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4'-

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(trifluorometil)bifenil-4-il]etil}-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-3-il)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4'-(trifluorometil)bifenil-3-il]etil}-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-metoxibifenil-3-il)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-metoxibifenil-4-il)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(3-bromofenil)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-pentil-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-piridin-4-ilfenil)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(*terc*-butil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-{[4'-(trifluorometil)bifenil-3-il]metil}-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(2,2-dimetilpropil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[(4'-etinilbifenil-3-il)metil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(3-piridin-2-ilbencil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(1,1-dimetil-2-feniletil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-hexil-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(1-metil-1-feniletil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(1,1,3,3-tetrametilbutil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(2-morfolin-4-iletil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(2-hidroxi-1,1-dimetiletil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-fluorofenil)e%l]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-clorofenil)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-tienil)etil]-L-α-glutamina,

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N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-clorofenil)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-(5-hidroxipentyl)-L-α-glutamina, ácido 3-[(bifenil-4-ilmetil)amino]-3-oxopropanóico, N^2-(bifenil-4-ilcarbonil)-N^1-propil-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-D-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(3-piridin-2-ilfenil)etil]-L-α-glutamina, N^2-2-naftoil-N^1-(3-fenilpropil)-L-α-glutamina, N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutamina, N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutamina, N^2-(4-fenoxibenzoil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-hexil-L-α-glutamina, N^2-(9*H*-fluoren-1-ilcarbonil)-N^1- hexil-L-α-glutamina, N^1-hexil-N^2-(4-fenoxibenzoil)-L-α-glutamina, N^1-hexil-N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-L-α-glutamina, N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-N^1-(3-fenilpropil)-L-α-glutamina, N^2-(4-fenoxibenzoil)-N^1-(3-fenilpropil)-L-α-glutamina, ácido *N*-[4-(pirimidin-2-ilamino)benzoil]-1-glutámico, ácido *N*-(1,1'-bifenil-4-ilcarbonil)-D-glutámico, *N*-[4-(pirimidin-2-ilamino)benzoil]-L-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-D-α-glutamina, N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-hidroxibutil)-L-α-glutamina, N^1-bencil-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina, N^1-bencil-N^2-[4-(pirimidin-2-

ilamino)benzoil]-L-α-glutamina, ácido (4S)-4-[(1,1'-bifenil-4-ilcarbonil)amino]-5-hidroxipentanóico, ácido *N*-({4'-[(fenilacetil)amino]-1,1'-bifenil-4-il}carbonil)-1-glutámico, ácido *N*-[(4'-{[(3-metil-1-benzofurano-2-il)carbonil]amino}-1,1'-bifenil-4-il)carbonil]-1-glutámico, ácido *N*-{[4'-(2-furoilamino)-1,1'-bifenil-4-il]carbonil}-1-glutámico, ácido *N*-{[4'-(acetilamino)-1,1'-bifenil-4-il]carbonil}-L-glutámico, ácido *N*-{[4'-(benzoilamino)-1,1'-bifenil-4-il]carbonil}-1-glutámico, ácido *N*-({4'-[(1-benzofurano-2-ilcarbonil)amino]-1,1'-bifenil-4-il}carbonil)-1-glutámico, N^1-(1,1-dimetil-2-feniletil)-N^2-(9H-fluoren-2-ilcarbonil)-L-α-glutamina, N^1-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-(9*H*-fluoren-2-ilcarbonil)-L-α-glutamina, N^2-(9H-fluoren-2-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutamina, N^1-(6-hidroxihexil)-N^2-(4-fenoxibenzoil)-L-α-glutamina, N^2-(9H-fluoren-9-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutaпúne, N^2-(9H-fluoren-9-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-(3-fenoxibenzoil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-(9H-fluoren-4-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina, N^1-1-adamantil-N^2-[(9-oxo-9H-fluoren-2-il)carbonil]-L-α-glutamina, N^1-1-adamantil-N^2-(4-fenoxibenzoil)-L-α-glutamina, N^1-1-adamantil-N^2-(9H-fluoren-2-ilcarbonil)-L-α-glutamina, N^1-1-adamantil-N^2-(9H-fluoren-9-ilcarbonil)-L-α-glutamina, N^2-(9H-fluoren-2-ilcarbonil)-N^1-(3-metilbencil)-L-α-glutamina, N^1-(3-metilbencil)-N^2-[(9-oxo-9H-fluoren-2-il)carbonil]-L-α-glutamina, N^2-(9H-fluoren-9-ilcarbonil)-N^1-(3-metilbencil)-L-α-glutamina, N^2-(9H-fluoren-2-ilcarbonil)-N^1-propil-L-α-glutamina, N^1-bencil-N^2-[(9-oxo-9H-fluoren-2-il)carbonil]-L-α-glutamina, N^1-bencil-N^2-(9H-

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fluoren-2-ilcarbonil)-L-α-glutamina, N^1-bencil-N^2-(9H-fluoren-9-ilcarbonil)-L-α-glutamina, N^1-bencil-N^2-(3-fenoxibenzoil)-L-α-glutamina, N^1-(1-metil-1-feniletil)-N^2-[(9-oxo-9H-fluoren-2-il)carbonil]-L-α-glutamina, N^2-(9H-fluoren-9-ilcarbonil)-N^1-(1-metil-1-feniletil)-L-α-glutamina, N^1-(1-metil-1-feniletil)-N^2-(3-fenoxibenzoil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[(1S)-1-feniletil]-L-α-glutamina, N^2-(9H-fluoren-2-ilcarbonil)-N^1-[(1S)-1-feniletil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[(1S)-1-(4-fluorofenil)etil]-L-α-glutamina, terc-butil N^2-(bifenil-4-ilcarbonil)-N^1-(1-feniletil)-L-α-glutaminato, N^2-(bifenil-4-ilcarbonil)-N^1-[(1R)-1-(4-fluorofenil)etil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[(1R)-1-feniletil]-L-α-glutamina, N^2-(9H-fluoren-2-ilcarbonil)-N^1-[(1R)-1-feniletil]-L-α-glutamina, N^2-(9H-fluoren-1-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutamina, N^1-(6-hidroxihexil)-N^2-[(9-oxo-9H-fluoren-2-il)carbonil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-9H-fluoren-9-il-L-α-glutamina, N^2-(9H-fluoren-2-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-[(3'-etoxibifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-[(2'-etoxibifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-[(4'-metoxibifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-(4-bromobenzoil)-N-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-[(3'-metoxibifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina, ácido 4'-{[((1S)-3-carboxi-1-{[(3,4,5-trimetoxibencil)amino]carbonil}propil)amino]carbonil}bifenil-3-carboxílico, N^2-[(4'-etilbifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina, N-bencil-N^2-[4-(2-

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naftil)benzoil]-L-α-glutamina, N^2-[(3',4'-dimetoxibifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-[(2',4'-dimetoxibifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, *N*-(3,4,5-trimetoxibencil)-N^2-[(3',4',5'-trimetoxibifenil-4-il)carbonil]-L-α-glutamina, *N*-(1-adamantilmetil)-N^2-(bifenil-4-ilcarbonil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(3'-metoxibifenil-4-il)carbonil]-L-α-glutamina, N^2-[(3',4'-dimetoxibifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(2'-etoxibifenil-4-il)carbonil]-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(3'-fluoro-4'-metilbifenil-4-il)carbonil]-L-α-glutamina, N^2-(4-bromobenzoil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, *N*-[(1S)-1-bencil-2-hidroxietil]-N^2-(bifenil-4-ilcarbonil)-L-α-glutamina, *N*-[(1S)-1-bencil-2-hidroxietil]-N^2-(9H-fluoren-2-ilcarbonil)-L-α-glutamina, *N*-(1-adamantilmetil)-N^2-(4-bromobenzoil)-L-α-glutamina, *N*-(1-adamantilmetil)-N^2-[(4'-hidroxibifenil-4-il)carbonil]-L-α-glutamina, N^2-[4-(1,3-benzodioxol-5-il)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, N^2-[(2',4'-dimetoxibifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, N^2-[(3'-fluoro-4'-metilbifenil-4-il)carbonil]-*N*-(3,4,5-tximetoxibencil)-L-α-glutamina, N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, *N*-(1-adamantilmetil)-N^2-({4'-[(3-metoxibencil)oxi]bifenil-4-il}carbonil)-L-α-glutamina, *N*-(1-adamantilmetil)-N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-*N*-metil-*N*-(2-feniletil)-L-α-glutamina, N^2-[(4'-sec-butilbifenil-4-il)carbonil]-*N*-

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(1,1-dimetil-2-feniletil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(4'-isopropilbifenil-4-il)carbonil]-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-(1,1':4',1''-terfenil-4-ilcarbonil)-L-α-glutamina, N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, N^2-[(4'-hidroxibifenil-4-il)carbonil]-*N*-(3,4,5-tximetoxibencil)-L-α-glutamina, *N*-(1-adamantilmetil)-N^2-({3'-[(dimetilamino)carbonil]bifenil-4-il}carbonil)-L-α-glutamina, *N*-(1-adamantilmetil)-N^2-[(3',5'-dimetilbifenil-4-il)carbonil]-L-α-glutamina, N^2-(9H-fluoren-2-ilcarbonil)-*N*-metil-*N*-(2-feniletil)-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(3'-metilbifenil-4-il)carbonil]-L-α-glutamina, N^2-({4'-[(3,5-dimetilbencil)oxi]bifenil-4-il}carbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-[(4'-{[3,5-bis(trifluorometil)bencil]oxi}bifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-[(3'-isopropilbifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-[(4'-isopropilbifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, *N*-(1-adamantilmetil)-N^2-[4-(1-benzofurano-5-il)benzoil]-L-α-glutamina, *N*-(1-adamantilmetil)-N^2-[4-(1H-indol-5-il)benzoil]-L-α-glutamina, N^2-[(3'-etoxibifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(3'-metoxibifenil-4-il)carbonil]-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(3'-isopropilbifenil-4-il)carbonil]-L-α-glutamina, N^2-[(3'-fluoro-4'-metilbifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-

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dimetiletil]-N^2-[(4'-isobutilbifenil-4-il)carbonil]-L-α-glutamina, N^2-(1,1':4'1''-terfenil-4-ilcarbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, *N*-bencil-N^2-{[3'-(hidroximetil)bifenil-4-il]carbonil}-L-α-glutamina, *N*-bencil-N^2-({4'-[(3-fluorobencil)oxi]bifenil-4-il}carbonil)-L-α-glutamina, *N*-bencil-N^2-{[4'-(benciloxi)bifenil-4-il]carbonil}-L-α-glutamina, *N*-bencil-N^2-[4-(feniletinil)benzoil]-L-α-glutamina, *N*-bencil-N^2-{4-[(9-hidroxi-9H-fluoren-9-il)etinil]benzoil}-L-α-glutamina, *N*-bencil-N^2-{4-[(1E)-3-oxo-3-fenilprop-1-en-1-il]benzoil}-L-α-glutamina, *N*-(3,4,5-trimetoxibencil)-N^2-[(2',4',6'-trimetilbifenil-4-il)carbonil]-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-({4'-[(3-metoxibencil)oxi]bifenil-4-il}carbonil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(4'-hidroxibifenil-4-il)carbonil]-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(3'-etoxibifenil-4-il)carbonil]-L-α-glutamina, N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-*N*-(6-hidroxihexil)-L-α-glutamina, N^2-({4'-[(3-metoxibencil)oxi]bifenil-4-il}carbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-(4-bromobenzoil)-*N*-(3-metilbencil)-L-α-glutamina, N^2-[4-(1,3-benzodioxol-5-il)benzoil]-*N*-(3-metilbencil)-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-*N*-butil-*N*-metil-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(4'-hidroxibifenil-4-il)carbonil]-L-α-glutamina, *N*-butil-N^2-(9H-fluoren-2-ilcarbonil)-*N*-metil-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-*N*-[2-(3,4-dimetoxifenil)etil]-*N*-metil-L-α-glutamina, N^2-[4-(1,3-benzodioxol-5-il)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-[2-(3,4-dimetoxifenil)etil]-N^2-

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(9H-fluoren-2-ilcarbonil)-*N*-metil-L-α-glutamina, N^2-(9H-fluoren-2-ilcarbonil)-*N*-[(2R)-2-fenilpropil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-*N*-[(2R)-2-fenilpropil]-L-α-glutamina, *N*-bencil-N^2-{4-[(4-hidroxiciclohexil)etinil]benzoil}-L-α-glutamina, N^2-{4-[(3-aminofenil)etinil]benzoil}-*N*-bencil-L-α-glutamina, *N*-bencil-N^2-[4-(3-hidroxi-3,3-difenilprop-1-in-1-il)benzoil]-L-α-glutamina, *N*-bencil-N^2-{4-[(3-metoxifenil)etinil]benzoil}-L-α-glutamina, N^2-[(3'-hidroxibifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-{[4'-(hidroximetil)bifenil-4-il]carbonil}-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(4'-metilbifenil-4-il)carbonil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-L-glutamamida, N^2-({4'-[(3-terc-butilfenoxi)metil]bifenil-4-il}carbonil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, N^2-({4'-[(3,5-di-terc-butilfenoxi)metil]bifenil-4-il}carbonil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-({4'-[(3-etilfenoxi)metil]bifenil-4-il}carbonil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-({4'-[(3-metoxifenoxi)metil]bifenil-4-il}carbonil)-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(3'-hidroxibifenil-4-il)carbonil]-L-α-glutamina, N^2-(bifenil-4ilcarbonil)-N^1-[2-(4-fluoropenil)-1,2-dimetiletil]-N^5-hidroxi-L-glutamanida, N^2-[4-(5-bromo-2-tienil)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-[2-(5-cloro-2-tienil)-1,1-dimetiletil]-N^2-[(3'-fluorobifenil-4-il)carbonil]-L-α-glutamina, N^2-[(3',4'-difluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-[2-(4-

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clorofenil)-1,1-dimetiletil]-N^2-[(3',4'-difluorobifenil-4-il)carbonil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(2',4'-difluorobifenil-4-il)carbonil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(2',5'-difluorobifenil-4-il)carbonil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(2',6'-difluorobifenil-4-il)carbonil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(3',5'-difluorobifenil-4-il)carbonil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(2',3'-difluorobifenil-4-il)carbonil]-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-(4-pirimidin-5-ilbenzoil)-L-α-glutamina, N^2-[(3',4'-difluorobifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, N^2-[(3',5'-difluorobifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, *N*-[2-(5-cloro-2-tienil)-1,1-dimetiletil]-N^2-[(3',4'-difluorobifenil-4-il)carbonil]-L-α-glutamina, N^2-(bifenil-4-ilcarbonil)-*N*-[2-(5-cloro-2-tienil)-1,1-dimetiletil]-L-α-glutamina, N^2-{[5-(3-cloro-4-fluorofenil)-2-tienil]carbonil}-*N*-[2-(5-cloro-2-tienil)-1,1-dimetiletil]-L-α-glutamina, N^2-{[4'-(hidroximetil)bifenil-4-il]carbonil}-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-{[4'-(bromometil)bifenil-4-il]carbonil}-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[4-(2-tienil)benzoil]-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[4-(2-furil)benzoil]-L-α-glutamina, N^2-{[4'-(hidroximetil)bifenil-4-il]carbonil}-*N*-(3-metilbencil)-L-α-glutamina, N^2-{[3'-(hidroximetil)bifenil-4-il]carbonil}-*N*-(3-metilbencil)-L-α-glutamina, N^2-[4-(2,3-dihidro-1-benzofurano-5-il)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-[(3'-

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cloro-4'-fluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-{[3'-(bromometil)bifenil-4-il]carbonil}-*N*-(3-metilbencil)-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[4-(3-tienil)benzoil]-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[4-(5-metil-2-tienil)benzoil]-L-α-glutamina, N^2-[4-(5-cloro-2-tienil)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(2-tienil)benzoil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-{[5-(3-metoxifenil)-2-tienil]carbonil}-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(5-fenil-2-tienil)carbonil]-L-α-glutamina, N^2-(2,2'-bitien-5-ilcarbonil)-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-[4-(2,3-dihidro-1-benzofuran-6-il)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-{[6-(3-metoxifenil)piridin-3-il]carbonil}-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(5-fenil-2-tienil)carbonil]-L-α-glutamina, N^2-[(3-fluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(5-piridin-4-il-2-tnienil)carbonil]-L-α-glutamina, N^2-{[5-(3-cloro-4-fluorofenil)-2-tienil]carbonil}-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(2,3-dihidro-1-benzofurano-6-il)benzoil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(5-piridin-3-il-2-tienil)carbonil]-L-α-glutamina, N^2-[4-(2,3-dihidro-1-benzofurano-6-il)benzoil]-*N*-(1,1-dimetil-2-

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feniletil)-L-α-glutamina, N^2-{[5-(3-cloro-4-fluorofenil)-2-tienil]carbonil}-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[4-(2-tienil)benzoil]-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-{[5-(3-metoxifenil)-2-tienil]carbonil}-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(5-fenil-2-tienil)carbonil]-L-α-glutamina, N^2-(2,2'-bitien-5-ilcarbonil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(5-piridin-4-il-2-tienil)carbonil]-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(5-piridin-3-il-2-tienil)carbonil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(5-cloro-2-tienil)benzoil]-L-α-glutamina, N^2-{[6-(5-cloro-2-tienil)piridin-3-il]carbonil}-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-(5-fenil-2-furoil)-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-{[6-(5-cloro-2-tienil)piridin-3-il]carbonil}-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-{[5-(3-metoxifenil)-2-tienil] carbonil}-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(5-piridin-3-il-2-tienil)carbonil]-L-α-glutamina, N^2-{[5-(3-cloro-4-fluorofenil)-2-tienil]carbonil}-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-(2,2'-bitien-5-ilcarbonil)-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(5-formil-2-tienil)benzoil]-L-α-glutamina, N^2-[4-(5-acetil-2-tienil)benzoil]-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-

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glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(1,3-tiazol-2-il)benzoil]-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[4-(1,3-tiazol-2-il)benzoil]-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-(5-fenil-2-furoil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[4-(5-formil-2-tienil)benzoil]-L-α-glutamina, N^2-[4-(5-acetil-2-tienil)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[3-(5-cloro-2-tienil)benzoil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[3-(2-tienil)benzoil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-{[5-(4-clorofenil)-2-tienil]carbonil}-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-{[5-(4-fluorofenil)-2-tienil]carbonil}-L-α-glutamina, N^2-[4-(5-bromo-2-tienil)benzoil]-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-[4-(5-bromo-2-tienil)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-{[5-(4-fluorofenil)-2-tienil]carbonil}-L-α-glutamina, N^2-[3-(5-cloro-2-tienil)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[3-(2-tienil)benzoil]-L-α-glutamina, N^2-[(3'-clorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-[(4'-clorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-[(4'-fluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-[(3'-fluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(3-fenil-2-tienil)carbonil]-L-α-glutamina, N^2-[(4'-clorobifenil-4-il)carbonil]-*N*-[2-(4-

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clorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-[(3'-clorobifenil-4-il)carbonil]-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-{[5-(4-fluorofenil)-2-tienil]carbonil}-L-α-glutamina, N^2-{[5-(4-clorofenil)-2-tienil]carbonil}-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(3-fenil-2-tienil)carbonil]-L-α-glutamina, N^2-(4-bromobenzoil)-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(4'-fluorobifenil-4-il)carbonil]-L-α-glutamina, *N*-(1,1-dimetil-2-feniletil)-N^2-[(3'-fluorobifenil-4-il)carbonil]-L-α-glutamina, N^2-[4-(5-cloro-2-tienil)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-D-α-glutamina, N^2-{[6-(5-cloro-2-tienil)piridin-3-il]carbonil}-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-{[5-(4-clorofenil)-2-tienil]carbonil}-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-{[5-(3,4-difluorofenil)-2-tienil]carbonil}-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, N^2-[(4'-{[3,5-bis(trifluorometil)fenoxi]metil}bifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina, N^2-({4'-[(1,3-benzodioxol-5-iloxi)metil]bifenil-4-il)carbonil)-*N*-(1,1-dimetil-1-feniletil)-L-α-glutamina, N^2-{[3'-(benciloxi)bifenil-4-il]carbonil}-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-({3'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-({3'-[(3-metoxibencil)oxi]bifenil-4-il}carbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina, N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina, *N*-bencil-N^2-

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{[4'-(bifenil-3-ilmetoxi)bifenil-4-il]carbonil}-L-α-glutamina, *N*-bencil-N^2-({4'-[(3'-metoxibifenil-3-il)metoxi]bifenil-4-il}carbonil)-L-α-glutamina, N^2-({4'-[(3,5-dimetoxifenoxi)metil]bifenil-4-il}carbonil)-*N*-(3-metilbencil)-L-α-glutamina, N^2-({3'-[(3,5-dimetoxifenoxi)metil]bifenil-4-il}carbonil)-*N*-(3-metilbencil)-L-α-glutamina, N^2-[(3'-{[3,5-bis(trifluorometil)fenoxi]metil}bifenil-4-il)carbonil]-*N*-(3-metilbencil)-L-α-glutamina, N^2-({3'-[(3-etilfenoxi)metil]bifenil-4-il}carbonil)-*N*-(3-metilbencil)-L-α-glutamina, *N*-bencil-N^2-{[4'-(bifenil-2-ilmetoxi)bifenil-4-il]carbonil}-L-α-glutamina, o *N*-bencil-N^2-({4'-[(3'-metoxibifenil-2-il)metoxi]bifenil-4-il}carbonil)-L-α-glutamina.

Métodos para la Elaboración de los Compuestos y Sales Farmacéuticamente Aceptables de Compuestos de la Invención

Los compuestos y sales farmacéuticamente aceptables de compuestos de la presente invención se pueden preparar utilizando una variedad de métodos partiendo de compuestos disponibles comercialmente, compuestos conocidos, o compuestos preparados por métodos conocidos. Las rutas sintéticas generales para muchos de los compuestos de la invención se incluyen en los siguientes esquemas. Esto se entiende por aquellos expertos en la técnica que las etapas de protección y desprotección no mostrados en los esquemas se pueden requerir para estas síntesis, y que el orden de las

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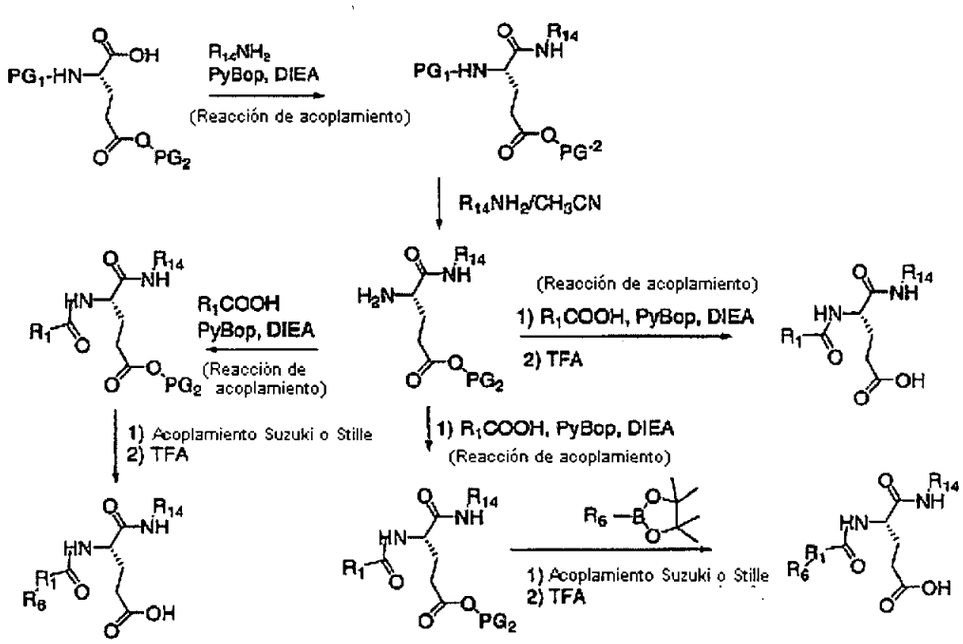
etapas se puede cambiar para acomodar la funcionalidad en la molécula objetivo.

Como se utiliza en los esquemas, PG_1 es un grupo protector amina; PG_2 es un grupo protector de ácido carboxílico; y R_1, R_2, R_6, R_{12}, R_{13}, R_{14}, y R_{15} son como se definió anteriormente.

Esquemas sintéticos generales para la preparación de compuestos



La formación amida entre un ácido carboxílico y una amina se lleva a cabo utilizando un reactivo de acoplamiento en un disolvente tal como DMF. Los reactivos de acoplamiento que se pueden utilizar incluyen hexafluorofosfato de benzotriazol-1-il-oxi-tris-(dimetilamino)-fosfonio (reactivo Bop), hexafluorofosfato de benzotriazol-1-il-oxi-tris-pirrolidino-fosfonio (reactivo PyBop), O-benzotriazol-N,N,N',N'-tetrametil-uronio-hexafluoro-fosfato (HBTU), clorhidrato de 1-(3-dimetilaminopropil)-3-etil-carbodiimida (EDC), y otros

reactivos de acoplamiento disponibles comercialmente o conocidos.

El acoplamiento cruzado se refiere generalmente a reacciones de acoplamiento como reacciones de acoplamiento Suzuki o Stille.

El grupo protector amina se cliva bajo condiciones suaves con una base amina para producir la amina libre. Se puede utilizar una variedad de bases amina, que incluyen por ejemplo, dietilamina, piperidina, morfolina, diciclohexilamina, p-dimetilaminopiridina, o diisopropiletilamina en un disolvente, tal como acetonitrilo o DMF.

La hidrólisis del grupo protector de ácido carboxílico se lleva a cabo utilizando TFA, NaOH, LiOH, carbonato de potasio, o similares.

El esquema 1 demuestra la preparación de compuestos de la invención en dos etapas a partir de dietil éster de *N*-(4-aminobenzoil)-1-glutámico (**1**). Se calienta un cloruro de arilo o heteroarilo tal como cloropiridina con dietil éster *N*-(4-aminobenzoil)-1-glutámico da el dietil éster (**2**), que se hidroliza con bases tales como NaOH, LiOH, o similares para proporcionar (**3**).

Esquema 1

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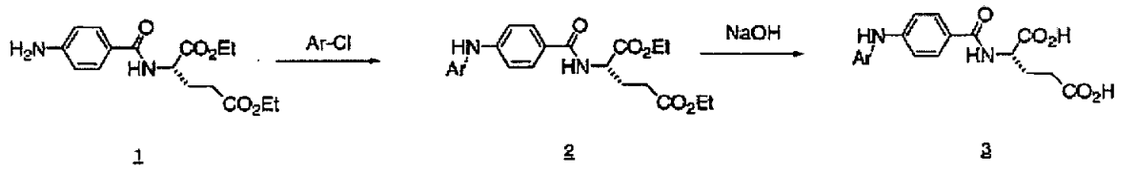
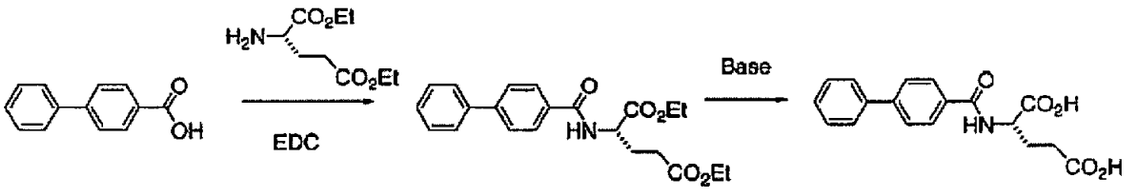


1 2 3

El Esquema 2 proporciona la preparación de un compuesto de la invención en dos etapas a partir de ácido bifenilcarboxílico (4). La formación de amida se lleva a cabo utilizando un reactivo de acoplamiento, tal como EDC. La hidrólisis del dietil éster (5) bajo condiciones básicas da el producto final ácido dicarboxílico (6).

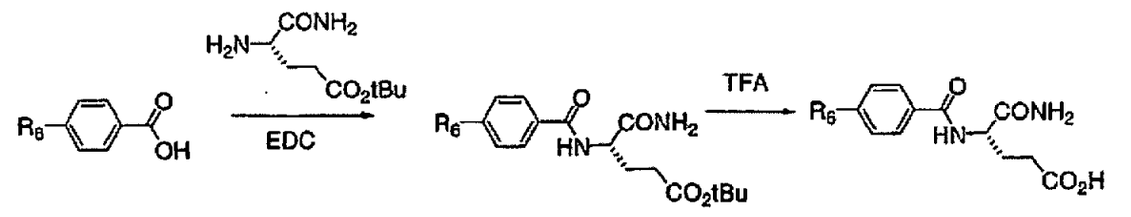
Esquema 2



4 5 6

El Esquema 3 proporciona la preparación de compuestos de la invención en dos etapas. El acoplamiento de la amina y el ácido carboxílico (7) se lleva a cabo utilizando un reactivo de acoplamiento tal como EDC. El grupo protector terc-butilo en (8) se hidroliza en condiciones acídicas (TFA en diclorometano) para proporcionar el producto (9).

Esquema 3



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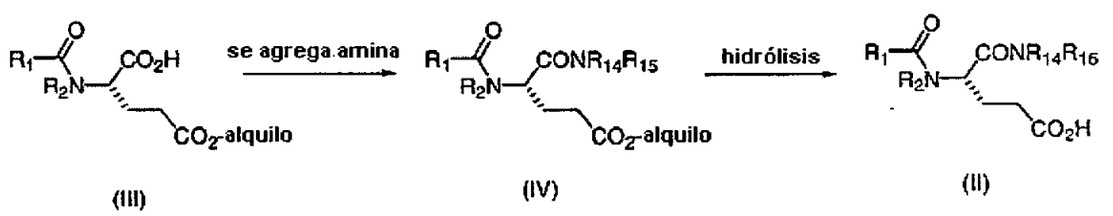
El Esquema 4 demuestra la síntesis de un compuesto o sal farmacéuticamente aceptable de un compuesto de la Fórmula (II). Como se muestra en el Esquema 4, un compuesto de la Fórmula (III) se trata con una amina bajo condiciones efectivas para proporcionar un compuesto de la Fórmula (IV). La hidrólisis el éster de alquilo proporciona un compuesto de la Fórmula (II).

Esquema 4



El Esquema 5 proporciona la síntesis de compuestos de la Fórmula (II) siguiendo los procedimientos generales establecidos en el esquema 4. El acoplamiento de aminas disponibles comercialmente, aminas conocidas en la literatura, u otras aminas con ácido bifenilcarboxílico (4, o ácido fluorencarboxílicos u otros ácidos carboxílicos) se pueden llevar a cabo en EDC, PyBop/DIEA, u otros reactivos de acoplamiento como se describió anteriormente en el esquema general. La hidrólisis del terc-butil éster (10) se lleva a cabo utilizando TFA. La segunda reacción de acoplamiento del ácido carboxílico (11) con una variedad de aminas se lleva a cabo utilizando un procedimiento similar como se emplea en la primera etapa. Finalmente, el metil éster (12) se hidroliza con NaOH/MeOH en THF para proporcionar (13).

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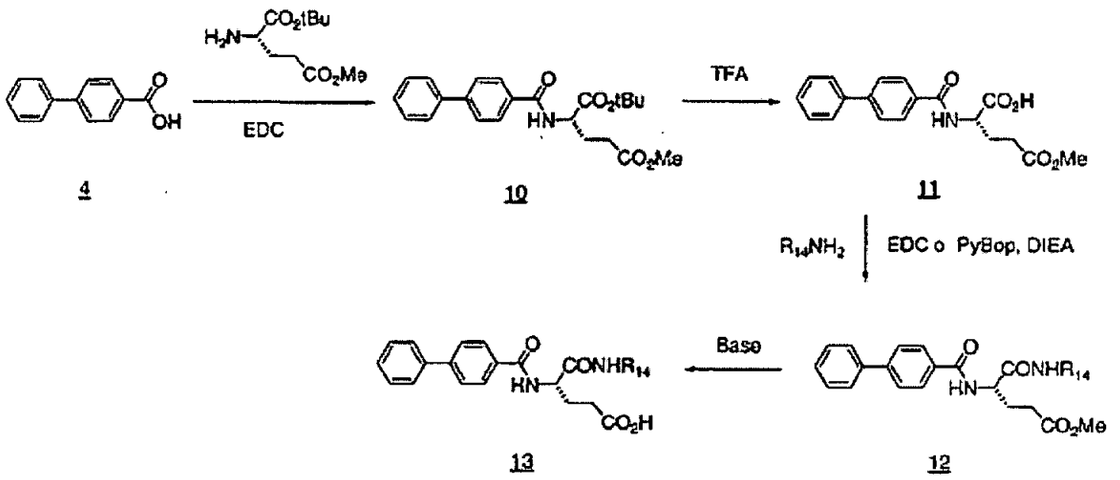
Esquema 5



El Esquema 6 demuestra la síntesis de un compuesto o sal farmacéuticamente aceptable de un compuesto de la Fórmula (II). Como se muestra en el Esquema 6, un compuesto de la Fórmula (V) se trata con una amina bajo condiciones efectivas para proporcionar un compuesto de la Fórmula (VI). La hidrólisis del grupo protector amina proporciona un compuesto de la Fórmula (VII), que se acopla con un ácido carboxílico bajo condiciones efectivas para proporcionar un compuesto de la Fórmula (VIII). La hidrólisis del ácido carboxílico protegido proporciona un compuesto de la Fórmula (II).

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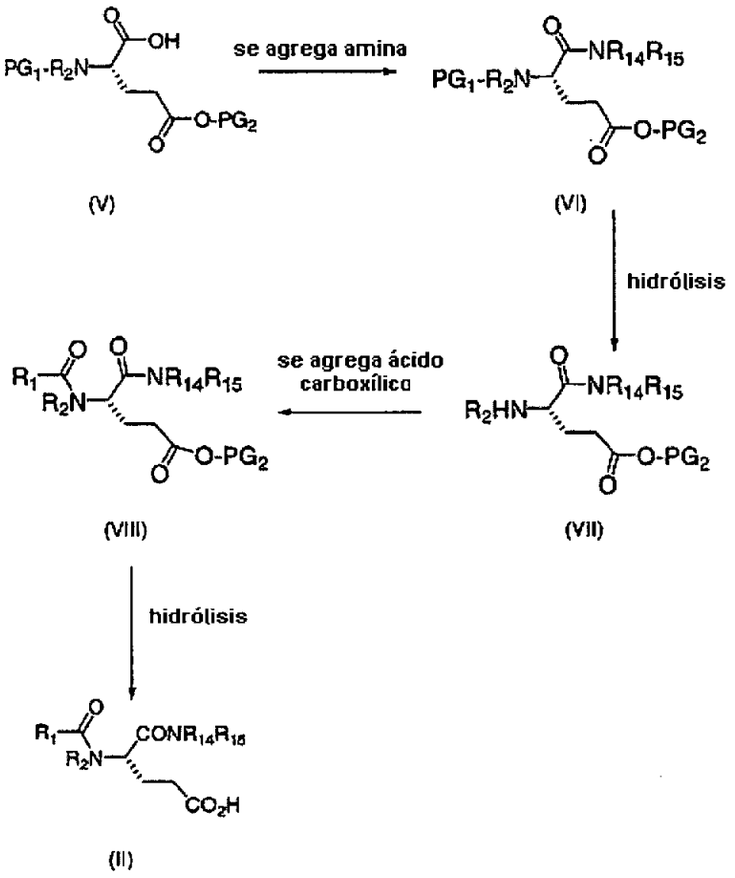
Esquema 6



El Esquema 7 proporciona la síntesis de compuestos de la Fórmula (II) siguiendo los procedimientos generales establecidos en el esquema 6. En el esquema 7, Fmoc-glu(Obut)OH (14) se hace reaccionar con una amina primaria o secundaria disponible comercialmente o conocida. La hidrólisis del grupo protector Fmoc de (15) se lleva a cabo con dietilamina en acetonitrilo. La amina (16) luego se acopla con un ácido carboxílico (por ejemplo ácido 4-bifenilcarboxílico o ácido fluorencarboxílico) y el terc-butil éster resultante (17) se hidroliza utilizando TFA en diclorometano para proporcionar (18).

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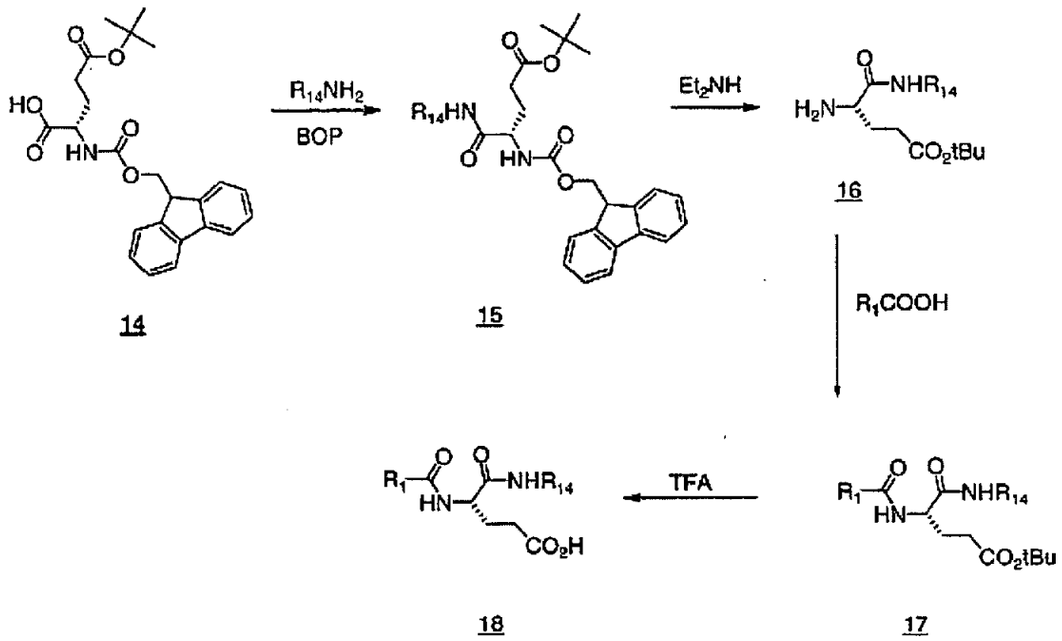
Esquema 7



El Esquema 8 demuestra la preparación de compuestos de la invención similar al procedimiento descrito en el esquema 7. Bromo o yodofenetilamina (o bromo o yodo bencilamina) se acopla con el aminoácido protegido Fmoc (14). La remoción del grupo protector Fmoc de (19) se lleva a cabo en base y el compuesto resultante (20) se hace reaccionar con ácido 4-bifenilcarboxílico (o ácido fluorencarboxílico u otro ácido carboxílico). El acoplamiento cruzado del intermedio bromo o yodo (21) con un éster borónico o reactivo de estanilo (por vía del método Suzuki o Stille) da el producto de acoplamiento t-butil éster (22), que luego se hidroliza para dar el producto de ácido carboxílico final (23).

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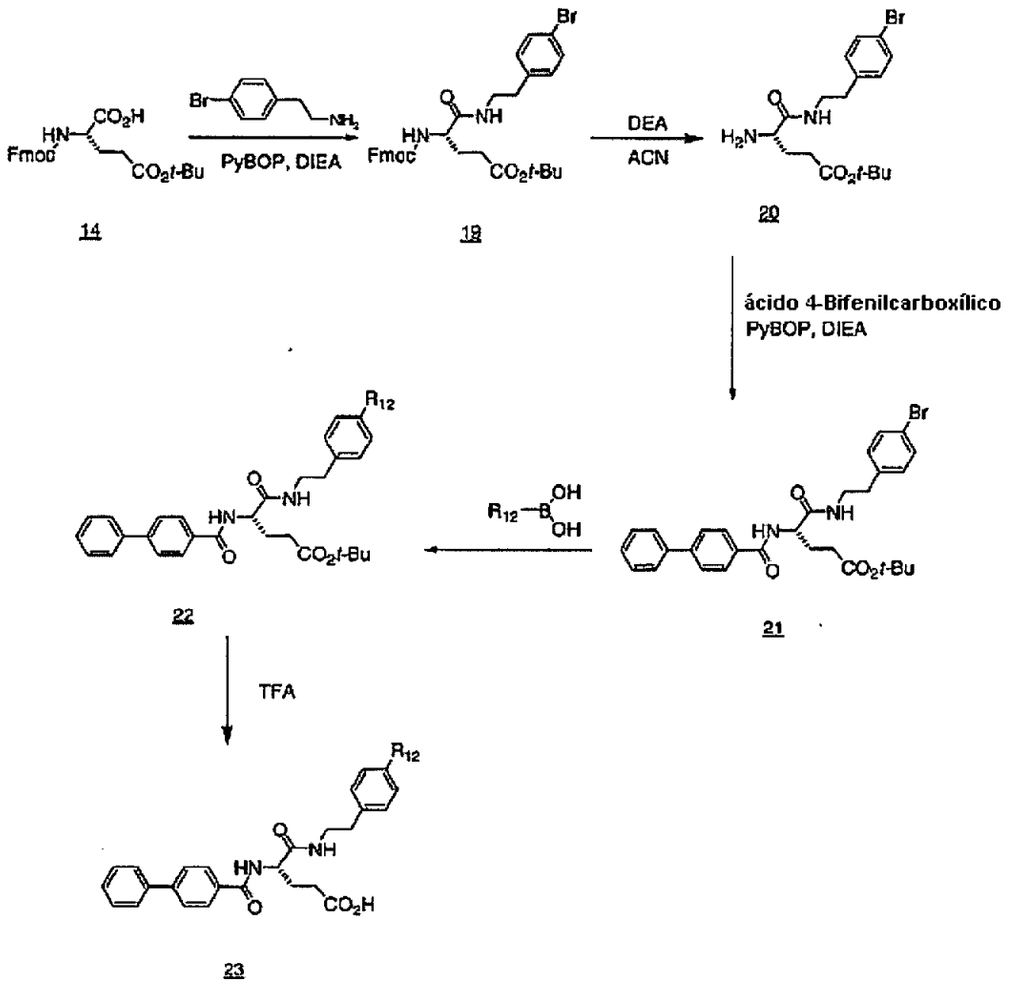
Esquema 8



El Esquema 9 demuestra la preparación de compuestos de la invención in tres etapas a partir de compuestos de bromo. El acoplamiento cruzado de (**25**) con un éster borónico o un compuesto de estanilo utilizando cualquier acoplamiento Suzuki o Stille da el terc-butil éster (**26**), que luego se hidroliza al ácido carboxílico (**27**).

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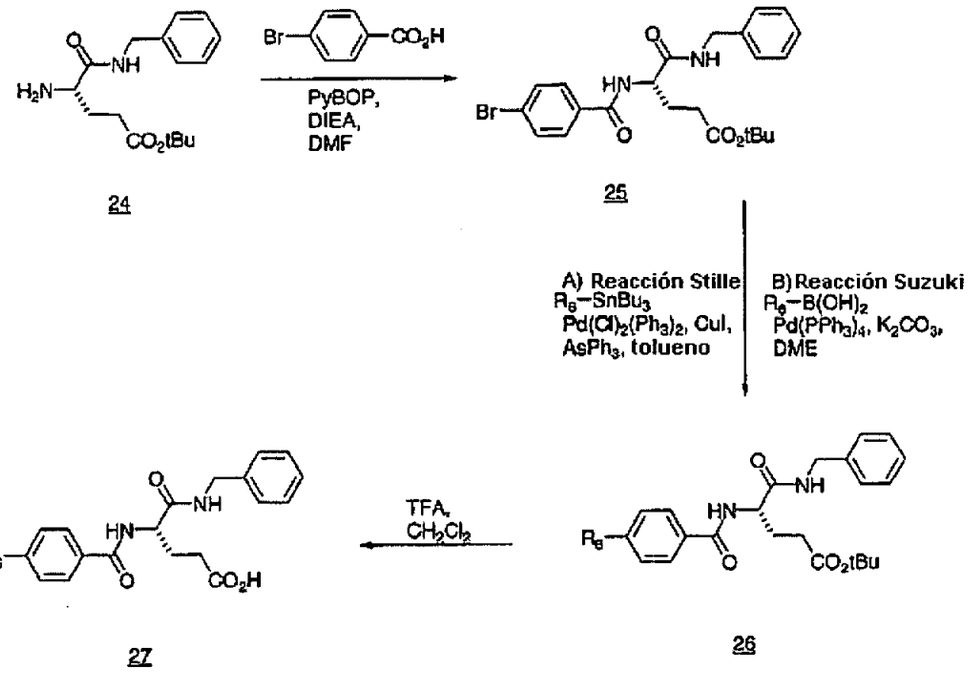
Esquema 9



El Esquema 10 proporciona compuestos de la invención preparados en tres o cuatro etapas a partir de compuestos de bromo. El acoplamiento Suzuki de (25) con el ácido 4-hidroxifenilborónico da el intermedio (28). La ruta A: Alquilación del compuesto fenólico con un alquilhaluro o haluro de bencilo proporciona (29), seguido por hidrólisis ácida para dar el ácido carboxílico (30). La ruta B: El compuesto brominado (31) se trata con un alcohol para dar (32), seguido por hidrólisis ácida para dar el ácido carboxílico (33). La ruta C: El intermedio (28) se trata un compuesto bromobencilbromuro para proporcionar (52), seguido por tratamiento con ácido fenilborónico para proporcionar (53), que luego se hidroliza ácido para dar (54).

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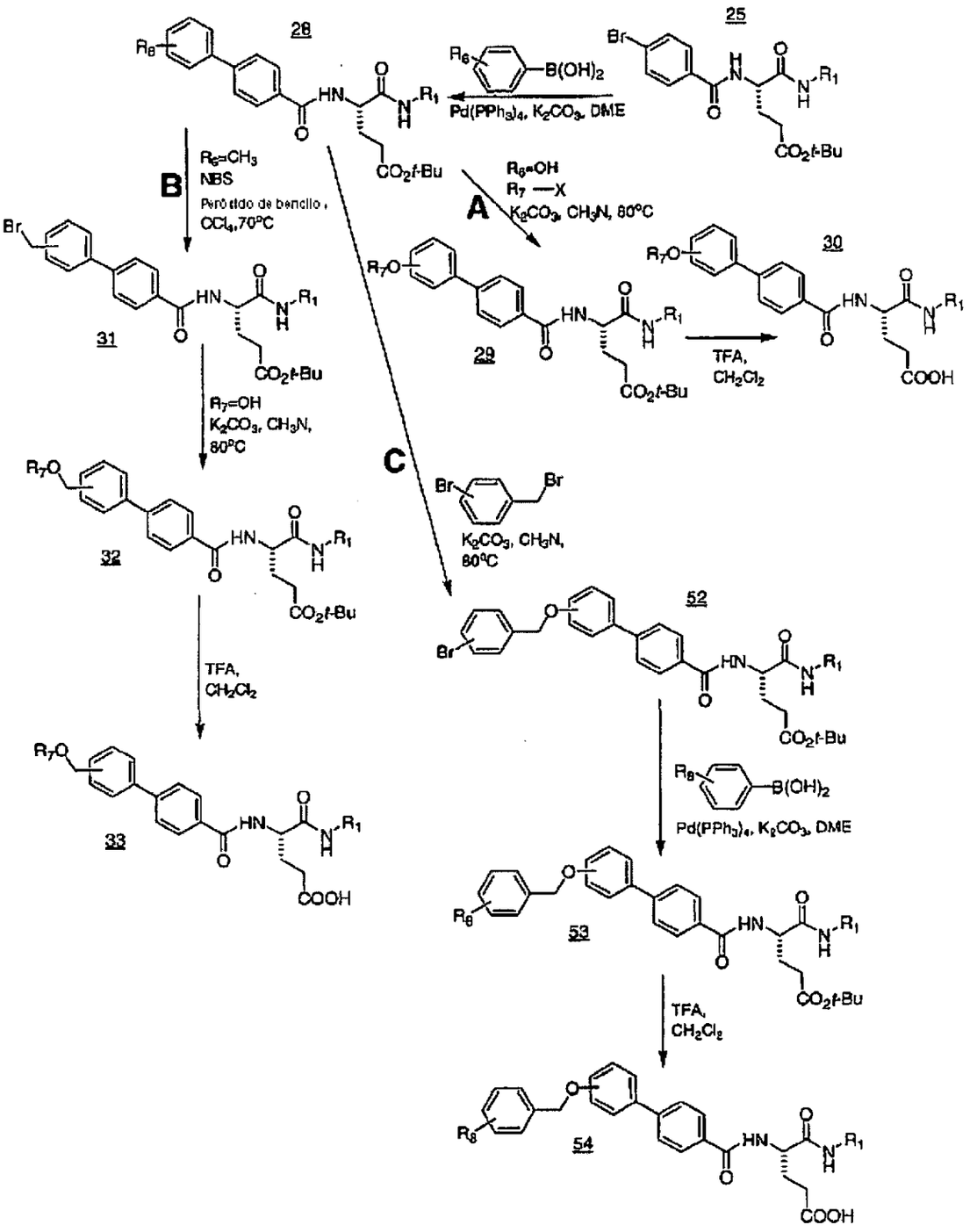
Esquema 10



El Esquema 11 proporciona compuestos de la invención preparados en una forma similar descrita en el esquema 10, excepto que se utiliza ácido 5-bromofuroico en la primera etapa de reacción de acoplamiento. El intermedio bromo (**34**) luego se hace reaccionar con un ácido borónico y la hidrólisis del terc-butil éster resultante (**35**) en ácido proporciona el ácido carboxílico (**36**).

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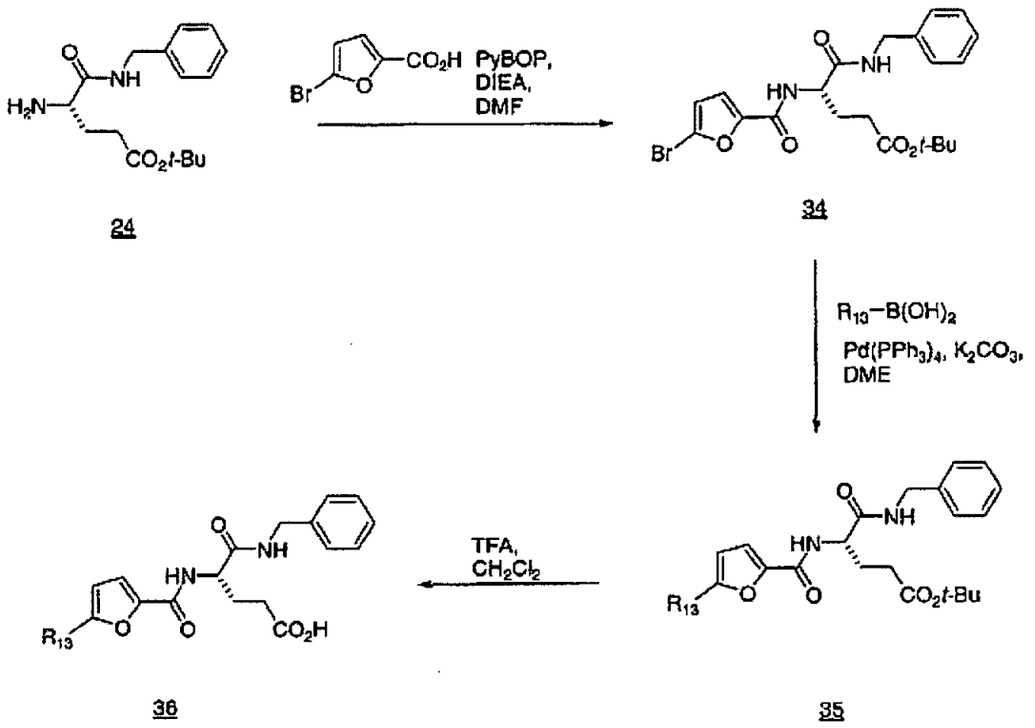
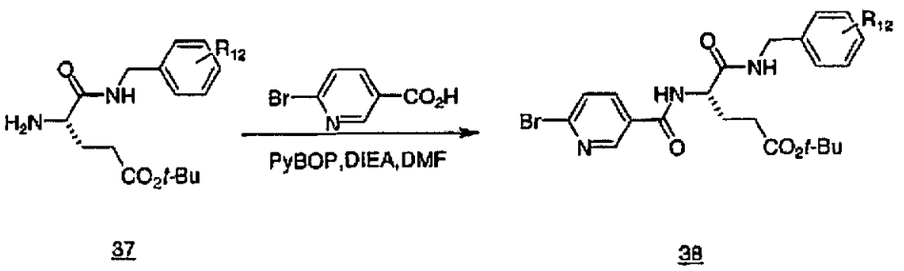
Esquema 11



24 34 36 35

El Esquema 12 proporciona compuestos de la invención preparados de acuerdo con el procedimiento descrito en el esquema 11, excepto que ácido 6-bromonicotínico se utiliza para acoplar con el intermedio amino (37) para producir (38).

Esquema 12



37 38

El Esquema 13 proporciona compuestos de la invención se prepara de acuerdo con el procedimiento descrito en el esquema 10, excepto que 4-(4,4,5,5)-tetrametil-1,3,2-dioxoborolan-2-il)anilina se utiliza en la reacción de

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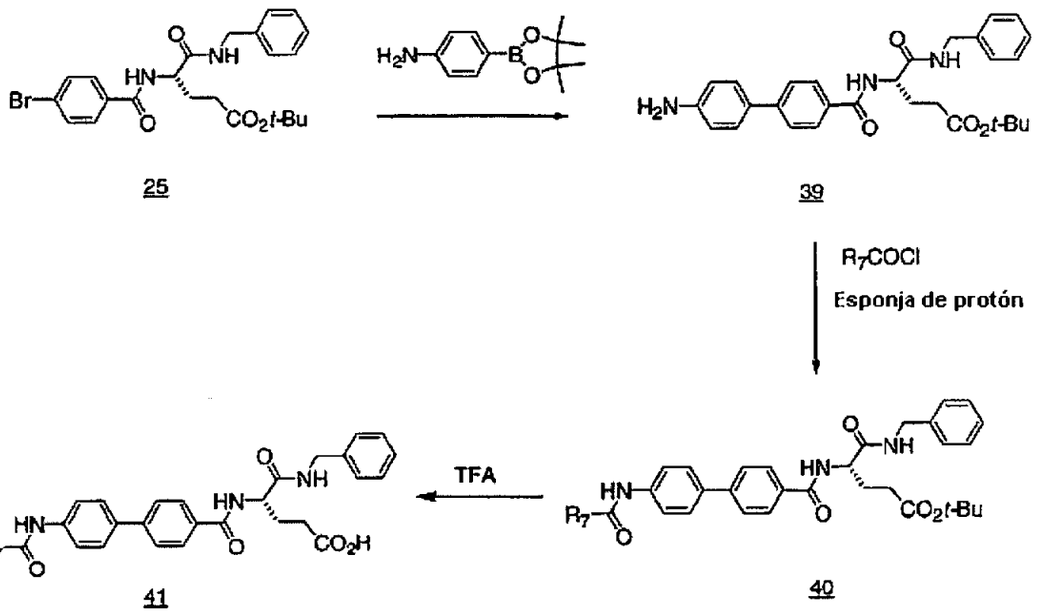
acoplamiento Suzuki con (25). El intermedio amino (39) luego se acila con un cloruro de ácido y el terc-butil éster (40) se hidroliza en condiciones acídicas para dar el ácido carboxílico deseado (41).

Esquema 13



El Esquema 14 demuestra la preparación de compuestos de la invención en cuatro etapas. El éster de α-terc-butil γ-etil éster de ácido l-glutámico se hace reaccionar con ácido 4-bifenilcarboxílico (4, u otro ácido carboxílico) utilizando EDC, PyBop, Bop, u otro agente de acoplamiento. La hidrólisis del terc-butil éster alfa (42) en ácido trifluoroacético da el intermedio alfa ácido carboxílico (43) en buen rendimiento. El tratamiento del ácido con una base (por ejemplo trietilamina) y cloroformato de etilo seguido por borohidruro de sodio da el alcohol correspondiente (44). El etil éster luego se hidroliza en condiciones básicas para dar el producto final (45).

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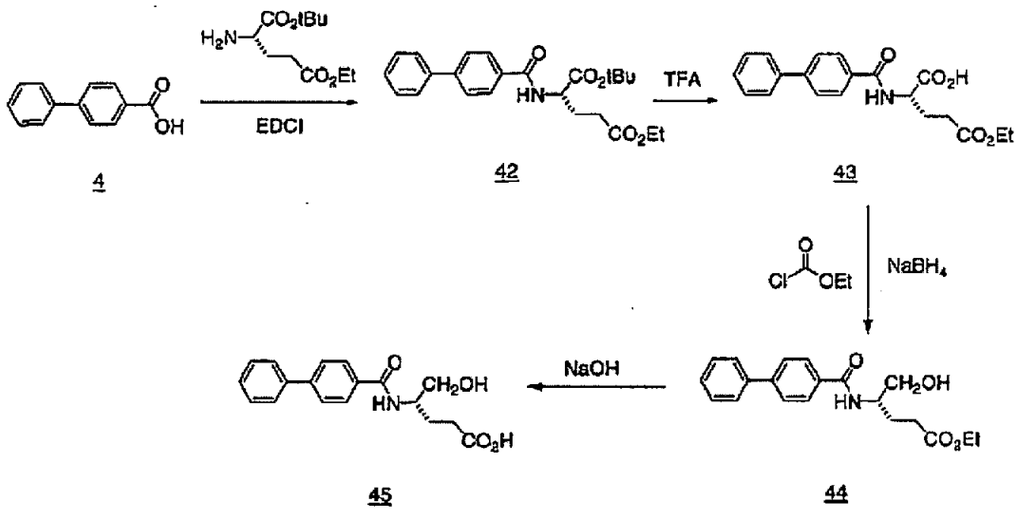
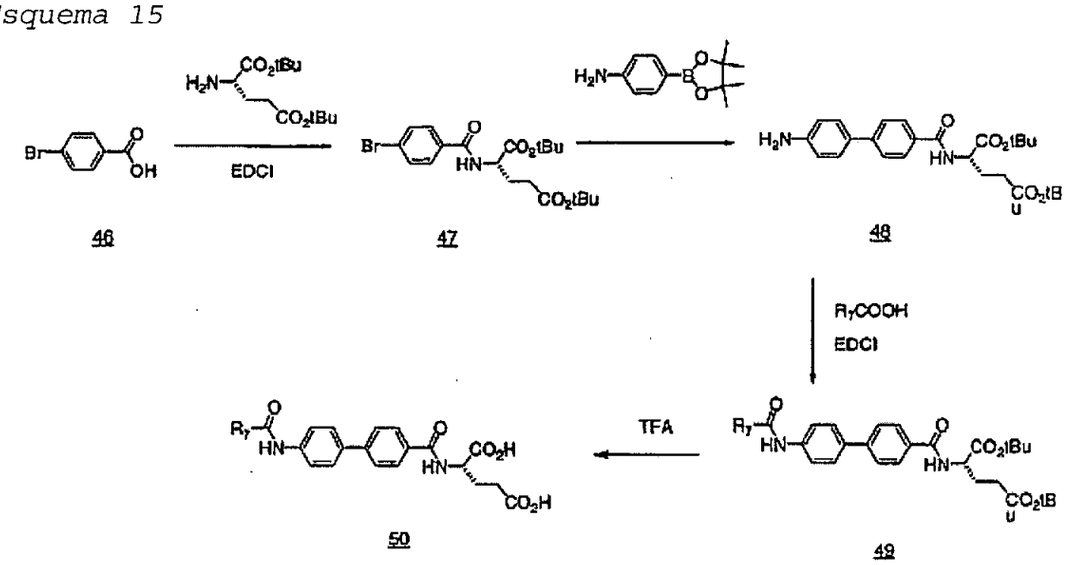
Esquema 14



El Esquema 15 proporciona compuestos de la invención preparados en cuatro etapas a partir de ácido bromobenzoico. Se acopla di-terc butil éster de ácido l-glutámico con el ácido bromobenzoico (**46**). El acoplamiento Suzuki del compuesto bromo (**47**) con 4-(4,4,5,5)-tetrametil-1,3,2-dioxoborolan-2-il)anilina da el intermedio amino (**48**) en buen rendimiento. La acilación de la amina con un cloruro de ácido da el producto acilado (**49**), y la hidrólisis del terc-butil éster en condiciones acídicas da el ácido dicarboxílico final (**50**).

Esquema 15



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El Esquema 16 proporciona los compuestos de la invención preparados en una única etapa a partir de un ácido carboxílico. Se hace reaccionar un ácido carboxílico de la invención (17) con Bop, clorhidrato de hidroxilamina, y DIEA para producir el ácido hidroxámico (51).

Esquema 16

17 51

Un experto en la técnica reconocerá que los esquemas 1-16 se pueden adaptar para producir otros compuestos y sales farmacéuticamente aceptables de compuestos de acuerdo con la presente invención.

Administración terapéutica

Cuando se administra a un animal, los compuestos o sales farmacéuticamente aceptables de los compuestos de la invención se pueden administrar puros o como un componente de una composición que comprende un portador fisiológicamente aceptable o vehículo. Una composición de la invención se puede preparar utilizando un método que comprende mezclar el compuesto o una sal farmacéuticamente aceptable del compuesto y un diluyente, excipiente o portador fisiológicamente aceptable. La mezcla se puede lograr utilizando los métodos bien conocidos para mezclar un compuesto o una sal

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farmacéuticamente aceptable del compuesto y un diluyente, excipiente o portador fisiológicamente aceptable.

Las actuales composiciones, que comprenden compuestos o sales farmacéuticamente aceptables de los compuestos de la invención se pueden administrar oralmente. Los compuestos o sales farmacéuticamente aceptables de los compuestos de la invención también se pueden administrar mediante cualquier otra ruta conveniente, por ejemplo, mediante infusión o inyección de bolo, por absorción a través de recubrimientos epiteliales o mucocutáneos (por ejemplo, mucosa oral, rectal, vaginal, e intestinal, etc.) y se pueden administrar junto con otros terapéuticos. La administración puede ser sistémica o local. Se pueden utilizar varios sistemas de suministro conocidos, que incluyen encapsulación en liposomas, micropartículas, microcápsulas, y cápsulas.

Los métodos de administración incluyen, pero no se limitan a, administración intradérmica, intramuscular, intraperitoneal, intravenosa, subcutánea, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdérmica, rectal, por inhalación, o tópica, particularmente a los oídos, nariz, ojos, o piel. En algunos casos, la administración resultará de la liberación del compuesto o una sal farmacéuticamente aceptable del compuesto en el torrente sanguíneo. La forma de administración se deja a discreción del médico.

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En una modalidad, el compuesto o una sal farmacéuticamente aceptable del compuesto se administran oralmente.

En otra modalidad, el compuesto o una sal farmacéuticamente aceptable del compuesto se administran intravenosamente.

En otra modalidad, puede ser deseable administrar el compuesto o una sal farmacéuticamente aceptable del compuesto localmente. Esto se puede lograr, por ejemplo, mediante infusión local durante cirugía, aplicación tópica, por ejemplo, simultáneamente con vendajes para heridas después de cirugía, por inyección, por medio de un catéter, por medio de un supositorio o edema, o por medio de un implante, dicho implante es de un material poroso, no poroso, o gelatinoso, que incluye membranas, tal como membranas sialáticas, o fibras.

En ciertas modalidades, puede ser deseable introducir el compuesto o una sal farmacéuticamente aceptable del compuesto en el sistema nervioso central, sistema circulatorio o tracto gastrointestinal mediante cualquier ruta adecuada, que incluye ruta intraventricular, inyección intratecal, inyección paraespinal, inyección epidural, enema, y por inyección adyacente al nervio periférico. La inyección intraventricular se puede facilitar mediante un catéter intraventricular, por ejemplo, unido a un reservorio, tal como un reservorio o malla.

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También se puede emplear la administración pulmonar, por ejemplo, mediante el uso de un inhalador o nebulizador, y la formulación con agente de aerosolización, o por vía de perfusión en un fluorocarbono o tensoactivo pulmonar sintético. En ciertas modalidades, el compuesto o una sal farmacéuticamente aceptable del compuesto se puede formular como un supositorio, con ligadores tradicionales y excipientes tal como triglicéridos.

En otra modalidad, el compuesto o una sal farmacéuticamente aceptable del compuesto se puede suministrar en una vesícula, en particular una liposoma (ver, Langer, Science 1990, 249, 1527-1533 y Treat et al., Liposomes in the Therapy of Infectious Disease and Cancer 1989, 317-327 y 353-365.

En aún otra modalidad, el compuesto o sal farmacéuticamente aceptable del compuesto se puede administrar en un sistema de liberación controlada o sistema de liberación sostenida (ver, por ejemplo, Goodson, in Medical Applications of Controlled Release 1984, vol. 2, 115-138). Se pueden utilizar Otros sistemas de liberación controlada o sostenida discutidos en la revisión por Langer, Science 1990, 249, 1527-1533. En una modalidad, se puede utilizar una bomba (Langer, Science 1990, 249, 1527-1533; Sefton, CRC Crit. Ref. Biomed. Eng. 1987, 14, 201; Buchwald et al., Surgery 1980, 88, 507; y Saudek et al., N. Engl. J Med. 1989, 321, 574). En otra modalidad. Los materiales poliméricos se pueden utilizar (ver, Medical Applications of Controlled Release (Langer and Wise, eds., 1974); Controlled Drug Bioavailability, Drug Product Design

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and Performance (Smolen and Ball, eds., 1984); Ranger and Peppas, J. Macromol. ScL Rev. Macromol. Chem. 1983, 2, 61; Levy et al., Science 1935, 228, 190; During et al., Ann. Neural. 1989, 25, 351; y Howard et al., J. Neurosurg. 1989, 71, 105).

En otra modalidad, un sistema de liberación controlada o sostenida se puede colocar en proximidad de un objetivo del compuesto o una sal farmacéuticamente aceptable del compuesto, por ejemplo, los órganos reproductores, requiriendo así solo una fracción de la dosis sistémica.

Las presentes composiciones pueden comprender opcionalmente una cantidad adecuada de un excipiente fisiológicamente aceptable.

Tales excipientes fisiológicamente aceptables pueden ser líquidos, tal como agua y aceites, que incluyen aquellos de petróleo, animal, vegetal o de origen sintético, tal como aceite de maní, aceite de soya, aceites minerales, aceite de sésamo y similares. Los excipientes fisiológicamente aceptables pueden ser solución salina, goma acacia, pasta de almidón, talco, queratina, sílice coloidal, urea y similares. Adicionalmente, se pueden utilizar agentes auxiliares, estabilizantes, espesantes, lubricantes, y colorantes. En una modalidad los excipientes fisiológicamente aceptables son estériles cuando se administran a un animal. El excipiente fisiológicamente aceptable debe ser estable bajo condiciones de fabricación y almacenamiento y se deben preservar contra

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la acción contaminante de microorganismos. El agua es un excipiente particularmente útil cuando el compuesto o una sal farmacéuticamente aceptable del compuesto se administra intravenosamente. Las soluciones salinas y la dextrosa acuosa y las soluciones de glicerol también se puede emplear como excipientes líquidos, particularmente para soluciones inyectables. Los excipientes fisiológicamente aceptables adecuados también incluyen almidón, glucosa, lactosa, sacarosa, gelatina, malta, arroz, harina, tiza, gel de sílice, estearato de sodio, monoestearato de glicerol, talco, cloruro de sodio, leche descremada seca, glicerol, propileno, glicol, agua, etanol, y similares. Las presentes composiciones, si se desea, también pueden contener cantidades menores de agentes humectantes o emulsificantes, o agentes de amortiguación del pH.

Se pueden utilizar portadores líquidos en la preparación de soluciones, suspensiones, emulsiones, jarabes, y elíxires. El compuesto o sal farmacéuticamente aceptable del compuesto de esta invención se puede disolver o suspender en un portador líquido farmacéuticamente aceptable tal como agua, un disolvente orgánico, una mezcla de ambos, o grasas o aceites farmacéuticamente aceptables. El portador líquido puede contener otros aditivos farmacéuticos que incluyen solubilizantes, emulsificantes, amortiguadores, preservantes, endulzantes, agentes saborizantes, agentes de suspensión, agentes espesantes, colores, reguladores de viscosidad, estabilizantes, o osmoreguladores. Ejemplos adecuados de portadores líquidos para administración oral y parenteral

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incluyen agua (particularmente que contiene aditivos como se mencionó anteriormente, por ejemplo, derivados de celulosa, que incluyen solución de carboximetilcelulosa de sodio), alcoholes (que incluyen alcoholes monohídricos y alcoholes polihídricos, por ejemplo, glicoles), y sus derivados, y aceites (por ejemplo, aceite de coco fraccionado y aceite de araquis). Para administración parenteral el portador puede ser un éster aceitoso tal como oleato de etilo y miristato de isopropilo. Los portadores líquidos estériles se utilizan en composiciones de forma líquida estéril para administración parenteral. El portador líquido para las composiciones presurizadas puede ser hidrocarburo halogenado u otro propulsor farmacéuticamente aceptable.

Las actuales composiciones pueden tomar la forma de soluciones, suspensiones, emulsiones, comprimidos, píldoras, pastillas, gránulos, cápsulas, cápsulas que contienen líquidos, polvos, formulaciones de liberación retardada, supositorios, emulsiones, aerosoles, suspensiones, o cualquier otra forma adecuada para uso. En una modalidad, la composición está en la forma de una cápsula. Otros ejemplos de excipientes fisiológicamente aceptables adecuados se describen en Remington's Pharmaceutical Sciences 1447-1676 (Alfonso R. Gennaro, ed., 19th ed. 1995).

En una modalidad, el compuesto o una sal farmacéuticamente aceptable del compuesto se formula de acuerdo con procedimientos de rutina como una composición adaptada para administración oral a humanos. Las composiciones para

suministro oral pueden estar en la forma de comprimidos, pastillas, formas bucales, píldoras, suspensiones acuosas o aceitosas o soluciones, gránulos, polvos, emulsiones, cápsulas, jarabes, o elíxires, por ejemplo. Las composiciones administradas oralmente pueden contener uno o más agentes, por ejemplo, agentes endulzantes tales como fructosa, aspartamo o sacarina; los agentes saborizantes tales como menta, aceite de menta, o cereza; agentes colorante; y agentes preservantes, para proporcionar una preparación farmacéuticamente agradable. En los polvos, el portador puede ser un sólido finamente dividido, que está en mezcla con el compuesto finamente dividido o sal farmacéuticamente aceptable del compuesto. En los comprimidos, el compuesto o sal farmacéuticamente aceptable del compuesto se mezcla con un portador que tiene las propiedades de compresión necesarias en proporciones adecuadas y compactado en la forma y tamaño deseado. Los polvos y tabletas pueden contener hasta aproximadamente 99% del compuesto o sal farmacéuticamente aceptable del compuesto.

Las cápsulas pueden contener mezclas de los compuestos o sales farmacéuticamente aceptables de los compuesto con llenadores inertes y/o diluyentes tales como almidones farmacéuticamente aceptables (por ejemplo, almidón d maíz, papa, o tapioca), azúcares, agentes endulzantes artificiales, celulosas en polvo (tal como celulosa cristalina y microcristalina), harinas, gelatinas, gomas, etc.

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La formulaciones de comprimido se pueden hacer por compresión convencional, granulación en húmedo, o métodos de granulación en seco y utiliza diluyentes farmacéuticamente aceptables, agentes aglutinantes, lubricantes, desintegrantes, agente modificadores de superficie (que incluyen tensoactivos), agentes de suspensión o estabilizantes (que incluyen, pero no se limitan a, estearato de magnesio, ácido esteárico, lauril sulfato de sodio, talco, azúcares, lactosa, dextrina, almidón, gelatina, celulosa, metilcelulosa, celulosa microcristalina, carboximetilcelulosa de sodio, carboximetilcelulosa de calcio, polivinilpirrolidina, ácido algínico, goma acacia, goma xantano, citrato de sodio, silicatos complejos, carbonato de calcio, glicina, sacarosa, sorbitol, fosfato de calcio, sulfato de calcio, lactosa, caolín, manitol, cloruro de sodio, ceras de baja fusión, y resinas de intercambio de ión. Los agentes modificadores de superficie incluyen agentes modificadores de superficie aniónica y no iónica. Ejemplos representativos de agentes modificadores de superficie incluyen, pero no se limitan a, poloxámero 188, cloruro de benzalconio, estearato de calcio, alcohol cetostearilo, ceras emulsificantes de cetomacrogol, ésteres de sorbitán, dióxido de silicio coloidal, fosfatos, dodecil sulfato de sodio, silicato de aluminio magnesio, y trietilamina.

Más aún, cuando en una forma de comprimido o píldora, las composiciones se pueden recubrir para retrasar la desintegración y absorción en el tracto gastrointestinal, proporcionando por lo tanto una acción sostenida durante un

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periodo de tiempo extendido. Selectivamente las membranas permeables que rodena un compuesto osmóticamente activo o una sal farmacéuticamente aceptable del compuesto también son adecuadas para composiciones administradas oralmente. En estas últimas plataformas, el fluido del ambiente que rodea la cápsula se pueden embeber por el compuesto, que se hincha para desplazar el agente o composición de agente a través de una abertura. Esta plataforma de suministro puede proporcionar un perfil de suministro del orden esencialmente cero opuesto a los perfiles pico de formulaciones de liberación inmediata. Un material de retraso en el tiempo tal como monoestearato de glicerol o estearato de glicerol se pueden utilizar. Las composiciones orales incluyen excipientes estándar tal como manitol, lactosa, almidón, estearato de magnesio, sacarina de sodio, celulosa, y carbonato de magnesio. En una modalidad los excipientes son de grado farmacéutico.

En otra modalidad, el compuesto o una sal farmacéuticamente aceptable del compuesto se puede formular para administración intravenosa. Típicamente, las composiciones para administración intravenosa comprenden amortiguador acuoso isotónico estéril. Cuando es necesario, las composiciones también pueden incluir un agente de solubilización. Las composiciones para administración intravenosa pueden incluir opcionalmente un anestésico tal como lignocaína para reducir el dolor en el sitio de la inyección, generalmente, los ingredientes se suministran solos o mezclados en forma de dosificación unitaria, por ejemplo, como un polvo seco

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liofilizado o concentrado libre de agua en un recipiente sellado herméticamente. tal como una ampolla o bolsa que indica la cantidad de agente activo. Cuando el compuesto o una sal farmacéuticamente aceptable del compuesto se administra por infusión, esta se puede dispensar, por ejemplo, con una botella de infusión que contiene agua estéril grado farmacéutico o solución salina. Cuando el compuesto o una sal farmacéuticamente aceptable del compuesto se administra por inyección, una ampolla de agua estéril para inyección o solución salina se pueden proporcionar de tal manera que los ingredientes se pueden mezclar antes de administración.

En otra modalidad, el compuesto o sal farmacéuticamente aceptable del compuesto se puede administrar transdérmicamente a través del uso de un parche transdérmico. La administración transdérmica incluyen administraciones a través de la superficie del cuerpo y los recubrimientos internos de los pasajes corporales que incluyen tejidos de mucosa y epiteliales. Tales administraciones se pueden llevar a cabo utilizando los compuestos actuales o sales farmacéuticamente aceptables de los compuestos, en lociones, cremas, espumas, parches, suspensiones, soluciones, y supositorios (por ejemplo, rectal o vaginal).

La administración transdérmica se puede lograr durante el uso de un parche transdérmico que contiene el compuesto o sal farmacéuticamente aceptable del compuesto y un portador que es inerte al compuesto o sal farmacéuticamente aceptable del

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compuesto, no es tóxico a la piel, y permite el suministro del agente para la absorción sistémica en el torrente sanguíneo por vía de la piel. El portador puede tomar cualquier número de formas tal como cremas o ungüentos, pastas, geles, o dispositivos oclusivos. Las cremas o ungüentos pueden ser emulsiones líquidas viscosas o semisólidas del tipo aceite en agua o agua en aceite. También pueden ser adecuadas Las pastas que comprenden polvos absorbentes dispersos en petróleo o petróleo hidrófilo que contiene el ingrediente activo. Una variedad de dispositivos oclusivos se puede utilizar para liberar el compuesto o sal farmacéuticamente aceptable del compuesto en el torrente sanguíneo, tal como una membrana semipermeable que cubre un reservorio que contiene el compuesto o sal farmacéuticamente aceptable del compuesto con o sin un portador, o una mezcla que contiene el ingrediente activo.

Los compuestos o sales farmacéuticamente aceptables de los compuestos de la invención se pueden administrar rectalmente o vaginalmente en la forma de un supositorio convencional. Las formulaciones de supositorios se pueden hacer a partir de materiales tradicionales, que incluyen manteca de cacao, con o sin la adición de ceras para alterar el punto de fusión del supositorio, y glicerina. Las bases de supositorio solubles en agua, tal como polietilenglicoles, de varios pesos moleculares, también se puede utilizar.

El compuesto o sal farmacéuticamente aceptable del compuesto se puede administrar mediante medios de liberación controlada

o liberación sostenida o por dispositivos de suministro que se conocen por aquellos expertos en la técnica. Tales formas de dosificación se pueden utilizar para proporcionar liberación controlada o sostenida de uno o más ingredientes activos utilizando, por ejemplo, hidroxipropilmetilcelulosa, u otras matrices de polímero, geles, membranas permeables, sistemas osmóticos, recubrimientos multicapa, micropartículas, liposomas, microesferas, o una combinación de estas para proporcionar el perfil de liberación deseado en proporciones variantes. Las formulaciones de liberación sostenida o controlada conocidas por aquellos expertos en la técnica, incluyen aquellas descritas aquí, se pueden seleccionar fácilmente para uso con ingredientes activos de la invención. La invención así abarca formas de dosificación unitarias únicas adecuadas para administración oral tal como, pero no limitadas a, tabletas, cápsulas, cápsulas de gel, y comprimidos oblongos que se adaptan para liberación controlada o sostenida.

En una modalidad una composición de liberación controlada o sostenida comprende una cantidad mínima del compuesto o una sal farmacéuticamente aceptable del compuesto para tratar o evitar un trastorno relacionado con metaloproteinasa en una cantidad mínima de tiempo. Las ventajas de las composiciones de liberación sostenida o controlada incluyen actividad extendida de la droga, frecuencia de dosificación reducida, y conformidad incrementada por el animal que se trata, adicionalmente las composiciones de liberación controlada o sostenida pueden afectar favorablemente el tiempo de inicio

de acción u otras características, tal como niveles de sangre del compuesto o una sal farmacéuticamente aceptables del compuesto, y pueden así reducir la ocurrencia de los efectos colaterales adversos.

Las composiciones de liberación controlada o incrementada pueden inicialmente liberar una cantidad del compuesto o una sal farmacéuticamente aceptable del compuesto que reduce rápidamente el efecto profiláctico o terapéutico deseado, y libera gradualmente y continuamente otras cantidades del compuesto o una sal farmacéuticamente aceptable del compuesto para mantener este nivel de efecto profiláctico o terapéutico durante un periodo extendido de tiempo. Para mantener un nivel constante del compuesto o una sal farmacéuticamente aceptable del compuesto en el cuerpo, el compuesto o una sal farmacéuticamente aceptable del compuesto se puede liberar de la forma de dosificación en una velocidad que reemplazará la cantidad del compuesto o una sal farmacéuticamente aceptable del compuesto que se metaboliza y se excreta del cuerpo. La liberación controlada o sostenida de un ingrediente activo puede ser estimulada por varias condiciones, que incluyen pero no se limitan a, cambios en el pH, cambios en la temperatura, concentración o disponibilidad de las enzimas, concentración o disponibilidad del agua, u otras condiciones fisiológicas o compuestos.

En ciertas modalidades, la actual invención se dirige a prodrogas de los compuestos o sales farmacéuticamente aceptables de los compuestos de la presente invención. Varias

formas de las prodrogas se conocen en la técnica, por ejemplo como se discute en Bundgaard, ed., Design of Prodrugs, Elsevier (1985); Widder et al., ed., Methods in Enzymology, vol. 4, Academic Press (1985); Kgrogsgaard-Larsen et al., ed., "Design and Application of Prodrugs", Textbook of Drug Design and Development, Chapter 5, 113-191 (1991); Bundgaard et al., Journal of Drug Delivery Reviews 1992, 8, 1-38; Bundgaard et al., J. Pharmaceutical Sciences 1988, 77, 285 et seq.; y Higuchi and Stella, eds., Prodrugs as Drug Delivery Systems, American Chemical Society (1975).

La cantidad del compuesto o una sal farmacéuticamente aceptable del compuesto es una cantidad que es efectiva para tratar o prevenir un trastorno relacionado con metaloproteinasas. En adición, los ensayos in Vitro, o in vivo se pueden emplear opcionalmente para ayudar a identificar los rangos de dosificación óptimos. La dosis precisa a ser empleada también puede depender de la ruta de administración, la afección, la seriedad de la afección a ser tratada, así como también varios factores físicos relacionados con el individuo a ser tratado, y se pueden decidir de acuerdo con el juicio de un médico. La dosificación equivalente se puede administrar durante varios periodos de tiempo que incluyen. Pero no se limitan a, aproximadamente cada dos horas, aproximadamente cada seis horas, aproximadamente cada ocho horas, aproximadamente cada doce horas, aproximadamente cada veinticuatro horas, aproximadamente cada treinta y seis, aproximadamente cada cuarenta y ocho horas, aproximadamente cada setenta y dos

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horas, aproximadamente cada semana, aproximadamente cada dos semanas, aproximadamente cada tres semanas, aproximadamente cada mes, y aproximadamente cada dos meses. El número y frecuencia de la dosificación corresponde a un curso completo de terapia que se determinará de acuerdo con el juicio de un médico. Las cantidades de dosificación efectiva descritas aquí se refieren a las cantidades totales administradas, que es, si más de un compuesto o sal farmacéuticamente aceptable del compuesto se administra, las cantidades de dosificación efectiva corresponden a la cantidad total administrada.

La cantidad del compuesto o una sal farmacéuticamente aceptable del compuesto que es efectiva para tratar o prevenir un trastorno relacionado con metaloproteinasas variará típicamente de aproximadamente 0.001 mg/kg a aproximadamente 250 mg/kg de peso corporal por día, en una modalidad, de aproximadamente 1 mg/kg a aproximadamente mg/kg de peso corporal por día, en otra modalidad, de aproximadamente 1 mg/kg a aproximadamente 50 mg/kg de peso corporal por día, y en otra modalidad, de aproximadamente 1 mg/kg a aproximadamente 20 mg/kg de peso corporal por día.

En otra modalidad, la composición farmacéutica está en forma de dosificación unitaria, por ejemplo, como un comprimido, cápsula, polvo, solución, suspensión, emulsión, gránulo, o supositorio. En tal forma, al composición se subdivide en dosis unitaria que contiene cantidades apropiadas del ingrediente activo; la forma de dosificación unitaria pueden ser composiciones empacadas, por ejemplo, polvos empacados,

frascos, ampollas, jeringas pre-llenas o bolsas que contienen líquidos. La forma de dosificación unitaria puede ser, por ejemplo, una cápsula o comprimido en sí mismo, o este puede ser el número apropiado de cualquiera de tales composiciones en forma de empaque. Tal forma de dosificación unitaria puede contener de aproximadamente 1 mg/kg a aproximadamente 250 mg/kg, y se puede dar en una dosis única o en dos o más dosis divididas.

El compuesto o una sal farmacéuticamente aceptable del compuesto se pueden ensayar in Vitro o in vivo para el efecto profiláctico antes de uso en humanos. También se pueden utilizar sistemas en modelos animales para demostrar la seguridad y eficacia.

Así, en una modalidad, la invención proporciona una composición que comprende unja cantidad efectiva del compuesto o una sal farmacéuticamente aceptable del compuesto de la presente invención y un portador farmacéuticamente aceptable.

En otra modalidad, el portador farmacéuticamente aceptable es adecuado para administración oral de la composición que comprende una forma de dosificación oral.

Usos profilácticos o terapéuticos

En una modalidad, los compuestos o sales farmacéuticamente aceptables de los compuestos de la presente invención son

útiles como moduladores de metaloproteinasa. De acuerdo con esto los compuestos y sales farmacéuticamente aceptables de los compuestos de la presente invención son útiles para tratar un animal con un trastorno relacionado con metaloproteinasa.

En una modalidad, la invención proporciona un método para tratar un trastorno relacionado con metaloproteinasas, que comprende administrar a un animal en necesidad de este un compuesto o una sal farmacéuticamente aceptable del compuesto de fórmula (I) o fórmula (II) en una cantidad efectiva para tratar un trastorno relacionado con metaloproteinasas. En otra modalidad. El compuesto o sal farmacéuticamente aceptable del compuesto es de la fórmula (Ia), (Ib), (Ic) o (Id).

En una modalidad, la metaloproteinasa es una metaloproteinasa de matriz o agrecanasa.

En otra modalidad, la agrecanasa es agrecanasa-1 o agrecanasa-2.

En una modalidad, el trastorno relacionado con metaloproteinasa se selecciona del grupo que consiste de trastornos artríticos, osteoartrítis, cáncer, artritis reumatoide, asma, enfermedad pulmonar obstructiva crónica, aterosclerosis, degeneración macular relacionada con la edad, infarto del miocardio, ulceración de córnea y otras enfermedades de superficie ocular, hepatitis, aneurismas

aórticas, tendonitis, enfermedades del sistema nervioso central, cicatrización anormal de heridas. Angiogénesis, reestenosis, cirrosis, esclerosis múltiple, glomerulonefritis, enfermedad de anfitrión Vs. Injerto, diabetes, enfermedad inflamatoria del intestino, choque, degeneración del disco intervertebral, apoplejía, osteopenia, y trastornos periodontales.

En otra modalidad, el trastorno relacionado con metaloproteinasa es osteoartritis.

En una modalidad, la presente invención se dirige a un método para modular la actividad de una metaloproteinasa en un animal en necesidad de este, que comprende poner en contacto la metaloproteinasa con una cantidad efectiva de un compuesto o sal farmacéuticamente aceptable del compuesto de fórmula (I) o fórmula (II). En una modalidad, el método comprende adicionalmente determinar la actividad de la metaloproteinasa. En una modalidad, la etapa de determinar la actividad de la metaloproteinasa se desarrolla antes de la etapa de poner en contacto la metaloproteinasa con el compuesto o una sal farmacéuticamente aceptable del compuesto. En otra modalidad, la etapa de determinar la actividad de la metaloproteinasa se desarrolla después de la etapa de poner en contacto la metaloproteinasa con el compuesto o una sal farmacéuticamente aceptable del compuesto. En otra modalidad, el compuesto o la sal farmacéuticamente aceptable del compuesto es de la fórmula (Ia), (Ib), (Ic), o (Id).

Los compuestos y sales farmacéuticamente aceptables de los compuestos de la fórmula (I) o fórmulas (II) son también útiles en la fabricación de medicamentos para tratar un trastorno relacionado con metaloproteinasa en un animal. En otra modalidad, el compuesto o sal farmacéuticamente aceptable del compuesto es de la fórmula Ia), (Ib), (Ic), o (Id).

De acuerdo con esto, en una modalidad, la invención proporciona el uso de un compuesto o sal farmacéuticamente aceptable del compuesto de fórmula (I) o fórmula (II) para la fabricación de un medicamento para tratar un trastorno relacionado con metaloproteinasa. En otra modalidad, el compuesto o sal farmacéuticamente aceptable del compuesto es de la fórmula Ia), (Ib), (Ic), o (Id).

En una modalidad, la metaloproteinasa es una matriz de metaloproteinasa o una agrecanasa.

En otra modalidad, la agrecanasa es agrecanasa-1 o agrecanasa-2.

En una modalidad, el trastorno relacionado con metaloproteinasa se selecciona del grupo que consiste de trastornos artríticos, osteoartritis, cáncer, artritis reumatoide, asma, enfermedad pulmonar obstructiva crónica, aterosclerosis, degeneración macular relacionada con la edad, infarto del miocardio, ulceración de córnea y otras

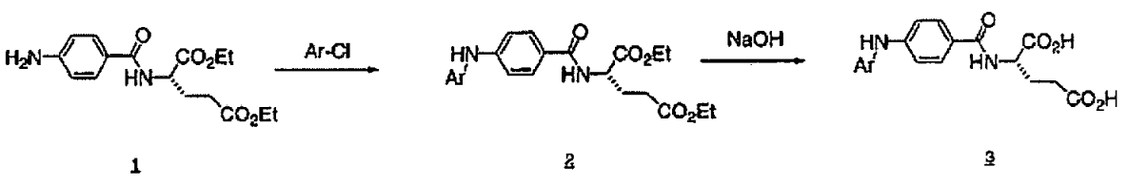
enfermedades de superficie ocular, hepatitis, aneurismas aórticas, tendonitis, enfermedades del sistema nervioso central, cicatrización anormal de heridas, Angiogénesis, reestenosis, cirrosis, esclerosis múltiple, glomerulonefritis, enfermedad de anfitrión Vs. Injerto, diabetes, enfermedad inflamatoria del intestino, choque, degeneración del disco intervertebral, apoplejía, osteopenia, y trastornos periodontales.

En otra modalidad, el trastorno relacionado con metaloproteinasa es osteoartritis.

En una modalidad, la presente invención se dirige al uso de un compuesto o sal farmacéuticamente aceptable del compuesto de fórmula (I) o fórmula (II) para la fabricación de un medicamento para modular la actividad de una metaloproteinasa. En una modalidad, el medicamento también es para determinar la actividad del receptor. En otra modalidad, el compuesto o sal farmacéuticamente aceptable del compuesto es de a fórmula Ia), (Ib), (Ic), o (Id).

Ejemplos

Esquema 1



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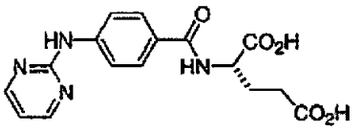
Ejemplo 1; ácido N-[4-(pirimidin-2-ilamino)benzoill-1-glutámico



Etapa A: dietil éster de ácido 2-[4-(pirimidin-2-ilamino)-benzoilamino]-pentanedióico

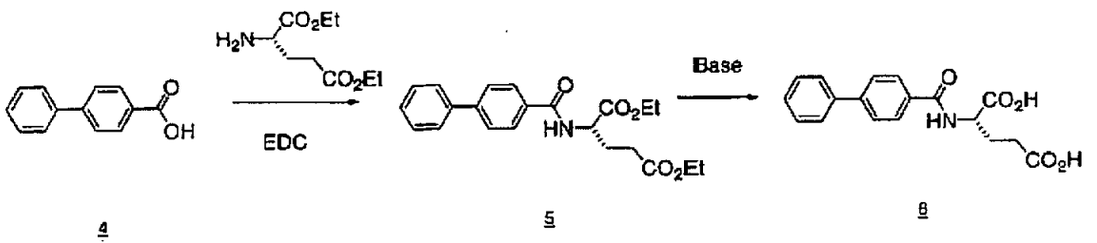
Se disuelven 2-Cloropirimidina (0.72 g, 6.3 mmol) y dietil éster de ácido N-(4-aminobenzoil)-1-glutámico (2.04 g, 6.3 mmol, 1 equiv.) en DMF (4 mL) y la mezcla resultante se calienta a 110°C durante 3 hrs. La reacción se completa como se determina mediante TLC. La mezcla se enfría a temperatura ambiente y se particiona entre acetato de etilo y agua. La fase orgánica se lava con solución salina, se seca sobre $MgSO_4$, y se concentra mediante rotavapor. El residuo se purifica mediante cromatografía de columna (gel de sílice, 50% de EtOAc/hexano) para producir 1.75 g del producto deseado dietil éster de ácido 2-[4-(pirimidin-2-ilamino)-benzoilamino]-pentanodióico en 69% de rendimiento. MS (ESI) m/z 399.

Etapa B: ácido N-[4-(pirimidin-2-ilamino)benzoil]-1-glutámico

Una solución de dietil éster de ácido 2-[4-(pirimidin-2-ilamino)-benzoilamino]-pentanedióico (250 mg, 0.62 mmol) en THF (4 mL) se agrega a MeOH (4 mL), seguido por la adición de solución de NaOH 1N (5 mL, 5 mmol, 8 equiv.). La mezcla se

agita a temperatura ambiente durante la noche. La reacción se completa como se determina mediante HPLC. Los disolventes se remueven mediante "rotavap" y se agrega una pequeña cantidad de agua (5 mL) para hacer una solución homogénea. Se agrega en forma de gota HCl 1N hasta que la solución alcanza un pH de 4. El precipitado sólido se recolecta mediante filtración, se lava con EtOAc, y se seca en un horno de vacío. El producto ácido N-[4-(pirimidin-2-ilamino)benzoil]-1-glutámico (120 mg) se aísla en 45% de rendimiento. MS (ESI) m/z 343.

Esquema 2



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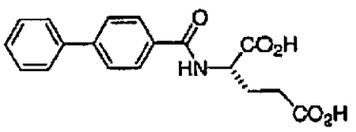
Ejemplo 2; ácido N-(1,1'-bifenil-4-ilcarbonil)-D-glutámico



Etapa A: dietil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanedióico

Una solución de ácido 4-bifenilcarboxílico (670 mg, 3.4 mmol) y (809 mg, 3.4 mmol, 1 equiv.) en DMF seco (20 mL) se agrega a EDCI (801 mg, 5.1 mmol, 1.5 equiv.), trietilamina (853 mg, 8.4 mmol, 2.5 equiv.) y DMAP (82 mg, 0.7 mmol, 20%). La mezcla se agita a temperatura ambiente durante la noche. La reacción se completa como se determina mediante TLC. La

mezcla se diluye con EtOAc y se lava con H_2O, solución salina, y se seca sobre sulfato de magnesio. El disolvente se remueve y el residuo se somete a cromatografía de columna (gel de sílice, 50% de EtOAc/hexano). 660 mg del producto dietil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanedióico deseado se aísla en 51% de rendimiento. MS (ESI) m/z 382.

Etapa B: ácido N-(1,1'-bifenil-4-ilcarbonil)-D-glutámico

Una solución de dietil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanedióico (250 mg, 0.65 mmol) en THF (6 mL) se agrega a MeOH (6 mL), seguido por la adición de solución de NaOH 1N (5.2 mL, 5.2 mmol, 8 eq.). La mezcla se agita a temperatura ambiente durante la noche. La reacción se completa como se determina mediante HPLC. Los disolventes se remueven mediante "rotavap" y una pequeña cantidad de agua (5 mL) se agrega para hacer una solución homogénea. Se agrega en forma de gota HCl 1N hasta que la solución alcanza un pH de 4. El precipitado sólido se recolecta mediante filtración, se lava con EtOAc, y se seca en un horno de vacío. El producto ácido N-(1,1'-bifenil-4-ilcarbonil)-D-glutámico (189 mg) se aísla en 89% de rendimiento. MS (ESI) m/z 326.

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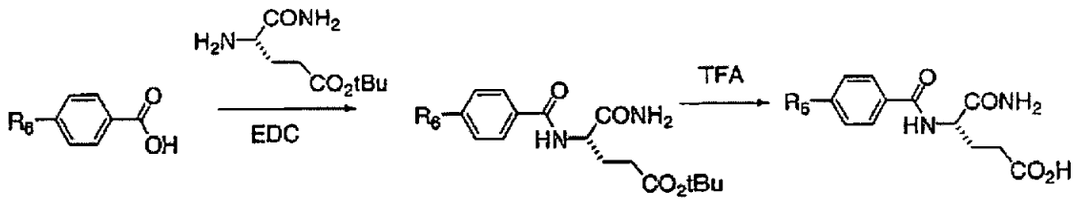
Esquema 3



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Ejemplo 3: *N*$^{\alpha}$-[4-(pirimidin-2-ilamino)benzoil]-1-alfa-glutamina

Etapa A: terc-butil éster de ácido 4-Carbamoil-4-[4-(pirimidin-2-ilamino)-benzoilamino]-butírico

Se disuelven ácido 4-(Pirimidin-2-ilamino)-benzoico (1.80 g, 8.4 mmol, 1 equiv.) y EDCI (2.41 g, 12.6 mmol, 1.5 equiv.) en DMF (60 mL) bajo N_2. La mezcla se agita a temperatura ambiente durante 20 minutos, seguido por la adición de H-Glu (OtBu)-NH_2 (2 g, 8.4 mmol, 1 equiv), Et_3N (2.92 mL, 20.9 mmol, 2.5 equiv.), y DMAP (0.512 g, 4.2 mmol, 0.5 equiv). La mezcla se le permite agitar a temperatura ambiente durante la noche. La reacción se completa como se determina mediante TLC. El DMF se remueve mediante "rotavap" y el residuo se disuelve en EtOAc. La capa orgánica se lava con solución salina y se seca sobre $MgSO_4$. La mayoría del disolvente se remueve mediante "rotavap" y un sólido se precipita a partir de la mezcla durante la evaporación del disolvente. El sólido se recolecta mediante filtración y se lava con EtOAc. Se obtiene 823 mg de terc-butil éster de ácido 4-Carbamoil-4-[4-(pirimidin-2-ilamino)-benzoilamino]-butírico en 25 % de rendimiento. MS (ESI) m/z 400.

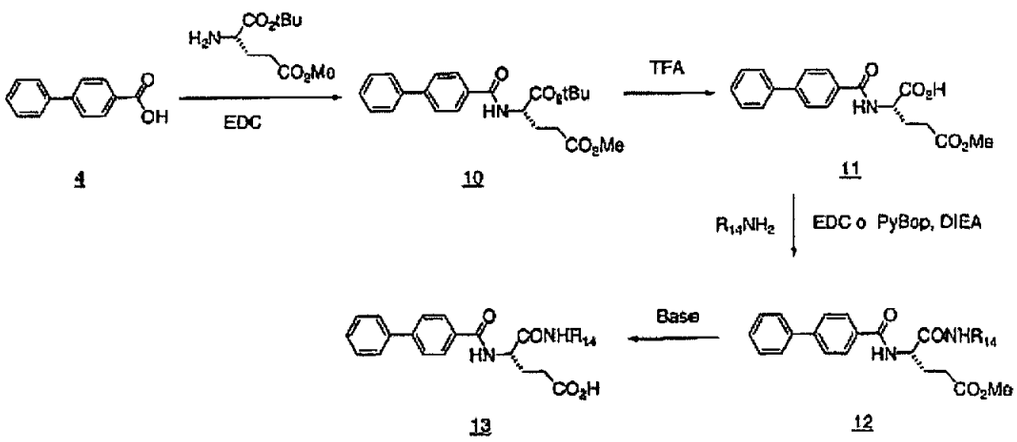
Etapa B: N^2-[4-(pirimidin-2-ilamino)benzoil]-1-alfa-glutamina

Se disuelve terc-butil éster de ácido 4-Carbamoil-4-[4-(pirimidin-2-ilamino)-benzoilamino]-butírico en dicloroetano (10 mL), seguido por la adición de TFA (5 mL). La mezcla se agita a temperatura ambiente durante 4 hrs. El TLC indica que la reacción se completa. Los disolventes luego se remueven mediante "rotavap" y el residuo se lava con EtOAc. Un sólido se recolecta mediante filtración y se seca en un horno de vacío durante la noche. Se obtiene ácido 4-Carbamoil-4-[4-(pirimidin-2-ilamino)-benzoilamino]-butírico en rendimiento cuantitativo (285 mg). MS (ESI) m/z 344.

Ejemplo 4: N^2-(1,1'-bifenil-4-ilcarbonil)-D-alfa-glutamina

El compuesto del título se prepara de acuerdo con los procedimientos similares a aquel descrito por el Ejemplo 3. Rendimiento 95%, MS (ESI) m/z 327.

Esquema 5



Ejemplo 5; N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-hidroxibutil)-L-alfa-glutamina

Etapa A: éster de 1-terc-butilo 5-metil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanedióico

Una solución de ácido 4-difenilcarboxílico (3.57 g, 18 mmol, 1.0 equiv.) en DMF (40 mL) se agrega a EDCI (4.28 g, 22.3 mmol, 1.24 equiv.) y se agita a temperatura ambiente durante 0.5 hrs. Se agrega H-Glu(OMe)Ot-Bu (5.02 g, 19.8 mmol, 1.1 equiv.), seguido por la adición de Et_3N (6.77 mL, 48.6 mmol, 2.7 equiv.) y DMAP (330 mg, 2.7 mmol, 15%). La mezcla se agita durante la noche bajo N_2. La reacción se completa como se determina mediante TLC. La mezcla de reacción se diluye con EtOAc, se lava con H_2O, luego solución salina. La capa orgánica se separa y luego se seca sobre $MgSO_4$. Después de concentración, el crudo se purifica mediante cromatografía de columna (Gel de sílice, 20% de EtOAc/Hexano) para producir 3.2 g de 1-terc-butil éster 5-metil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanedióico en 44.7% de rendimiento. MS (ESI) m/z 396.

Etapa B: 5-metil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanedióico

Una solución de éster de 1-terc-butilo 5- metil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanodióico (1.5 g, 3.8 mmol) en dicloroetano (26 mL) se agrega a TFA (13 mL) a temperatura ambiente. La mezcla se agita durante 4 hrs. y El TLC indica que la reacción se completa. El disolvente se remueve mediante rotavapor. El sólido así obtenido se seca

bajo vacío para proporcionar 1.128 g de 5- metil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanodióico [G9591-161-1] en 87% de rendimiento. MS (ESI) m/z 342.

Etapa C: metil éster de ácido 4-[(Bifenil-4-carbonil)-amino]-4-(4-hidroxi-butilcarbamoyl)- butirico

Una solución de 5-metil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanodióico (400 mg, 1.2 mmol, 1 equiv.) en DMF (10 mL) se agrega a EDCI (337 mg, 1.8 mmol, 1.5 equiv.). La solución se agita a temperatura ambiente bajo N_2 durante 40 min. Se agrega 4-Amino-1-butanol (0.11 mL, 1.2 mmol, 1 equiv.), seguido por addición de Et_3N (0.41 mL, 2.9 mmol, 2.5 equiv.) y DMAP (72 mg, 0.59 mmol, 0.5 equiv.). La mezcla se agita durante la noche bajo N_2. La mezcla de reacción luego se vierte en agua fría y un sólido se precipita a partir de la solución. El sólido se recolecta mediante filtración y se seca bajo vacío para dar 229 mg de metil éster de ácido 4-[(Bifenil-4-carbonil)-amino]-4-(4-hidroxi- butilcarbamoil)-butírico en 47% de rendimiento. MS (ESI) m/z 413.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-hidroxibutil)-1-alfa-glutamina

Una solución de metil éster de ácido 4-[(Bifenil-4-carbonil)-amino]-4-(4-hidroxi-butilcarbamoil)-butírico (229 mg, 0.56 mmol, 1 equiv.) en THF (10 mL) y MeOH (2.8 mL) se agrega a NaOH 1N (2.8 mL, 2.8 mmol, 5 equiv.). La solución se agita a

temperatura ambiente durante 2.5 hrs. Después el TLC indica que la reacción se completa, el disolvente se evapora y el residuo se disuelve en H_2O. Después de ajusta el pH de la solución a 3 utilizando HCl 1N, un sólido se precipita a partir de la solución. El sólido se recolecta mediante filtración y se lava con agua. Después de secar, 120 mg de N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-hidroxibutil)-1-alfa-glutamina se aísla en 54.1% de rendimiento. MS (ESI) m/z 399.

Ejemplo 6:

Los siguientes compuestos se preparan de acuerdo con los procedimientos similares a aquellos descritos en el Ejemplo 5.

Ejemplo 6A; N^2-(1,1'-bifenil)-4-ilcarbonil)-N1-2,3-dihidro-1*H*-inden-1-il-L-α-glutamina

Etapa C: metil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-2,3-dihidro-1*H*-inden-2-il-L-α-glutaminato

Como se describió anteriormente de acuerdo con el procedimiento en el Ejemplo 5, excepto que PyBop/DIEA (o Bop/DIEA) se utiliza. MS (ESI) m/z 457.2; MS (ESI) m/z 913.4; HRMS: calculado para $C_{28}H_{28}N_2O_4$ + H+, 457.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 457.21403.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-2,3-dihidro-1*H*-inden-2-il-L-α-glutamina

400

MS (ESI) m/z 441.2; MS (ESI) m/z 883.3; HRMS: calculado para $C_{27}H_{26}N_2O_4$ + H+, 443.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 443.19699.

Ejemplo 6B: N^2-(bifenil-4-ilcarbonil)-N^1-(2-hidroxi-1,1-dimetiletil)-L-α-glutamina

Etapa C: metil N^2-(bifenil-4-ilcarbonil)-N^1-(2-hidroxi-1,1-dimetiletil)-L-α-glutaminato

Como se describió anteriormente de acuerdo con el procedimiento en el Ejemplo 5, excepto que se utiliza PyBop/DIEA (o Bop/DIEA). MS (ESI) m/z 413.1; MS (ESI) m/z 825.2; HRMS: calculado para $C_{23}H_{28}N_2O_5$ + H+, 413.20710; encontrado (ESI-FTMS, $[M+H]^{1+}$), 413.20705.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(2-hidroxi-1,1-dimetiletil)-L-α-glutamina

MS (EST) m/z 399.1; MS (ESI) m/z 797.3; HRMS: calculado para $C_{22}H_{26}N_2O_5$ + H+, 399.19145; encontrado (ESI-FTMS, $[M+H]^{1+}$), 399.19217.

Ejemplo 6C; N^2-(bifenil-4-ilcarbonil)-N^1-(1,1.3.3-tetrametilbutil)-L-α-glutamina

Etapa C: metil N^2-(bifenil-4-ilcarbonil)-N^1-(1,1,3,3-tetrametilbutil)-L-α-glutaminato

Como se describió anteriormente de acuerdo con el procedimiento en el Ejemplo 5, excepto que se utiliza PyBop/DIEA (o Bop/DIEA). MS (ESI) m/z 453.2; MS (ESI) m/z 905.4; HRMS: calculado para $C_{27}H_{36}N_2O_4$ + H+, 453.27478; encontrado (ESI-FTMS, $[M+H]^{1+}$), 453.27588.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(1,1,3,3-tetrametilbutil)-L-α-glutamina

MS (ESI) m/z 439.2; MS (ESI) m/z 877.4; HRMS: calculado para $C_{26}H_{34}N_2O_4$ + H+, 439.25913; encontrado (ESI-FTMS, $[M+H]^{1+}$), 439.25974.

Ejemplo 6D: N^1-(1,1-dimetil-2-feniletil)-N^2-(9*H*-fluoren-2-ilcarbonil)-L-α-glutamina

Etapa A: 1-terc-butil 5-metil-*N*-(9*H*-fluoren-2-ilcarbonil)-1-glutamato

Como se describió anteriormente de acuerdo con el procedimiento en el Ejemplo 5, excepto que se utiliza ácido 2-fluorenocarboxílico. MS (ESI) m/z 410.2; MS (ESI) m/z 819.4; HRMS: calculado para $C_{24}H_{27}NO_5$ +Na+, 432.17814; encontrado (ESI-FTMS, $[M+Na]^{1+}$), 432.17902.

Etapa B: ácido (2S)-2-[(9H-fluoren-2-ilcarbonil)amino]-5-metoxi-5- oxopentanóico

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MS (ESI) m/z 354.1; MS (ESI) m/z 707.3; HRMS: calculado para $C_{20}H_{19}NO_5$ + H+, 354.13360; encontrado (ESI-FTMS, $[M+H]^{1+}$), 354.13428.

Etapa C: metil N^1-(1,1-dimetil-2-feniletil)-N^2-(9*H*-fluoren-2-ilcarbonil)-L-α-glutaminato

MS (ESI) m/z 485.3; MS (ESI) m/z 969.5; MS (ESI) m/z 507.3; HRMS: calculado para $C_{30}H_{32}N_2O_4$+ Na+, 507.22543; encontrado (ESI-FTMS, $[M+Na]^{1+}$), 507.22863.

Etapa D: N^1-(1,1-dimetil-2-feniletil)-N^2-(9*H*-fluoren-2-ilcarbonil)-L-α-glutamina

MS (ESI) m/z 471.3; MS (ESI) m/z 941.5.

Ejemplo 6E; N^1-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-(9*H*-fluoren-2-ilcarbonil)-L-α-glutamina

Etapa A: Como se describió anteriormente de acuerdo con el procedimiento en el Ejemplo 5, excepto que se utiliza ácido 2-fluorenocarboxílico.

Etapa C: metil N^1-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-(9*H*-fluoren-2-ilcarbonil)-L-α-glutaminato

MS (ESI) m/z 519.2; MS (ESI) m/z 1037.5; HRMS: calculado para $C_{30}H_{31}ClN_2O_4$ + H+, 519.20451; encontrado (ESI-FTMS, $[M+H]^{1+}$), 519.20406.

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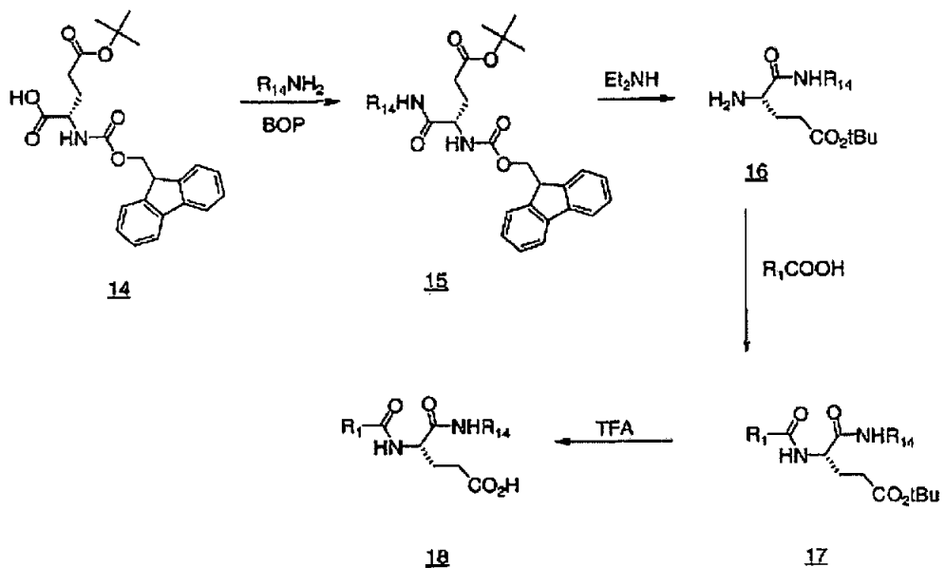
Etapa D: N^1-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-(9*H*-fluoren-2-ilcarbonil)-L-α-glutamina

MS (ESI) m/z 505.2; MS (ESI) m/z 1009.5.

Esquema 7



Ejemplo 7: N^1-(1,3-benzodioxol-5-ilmetil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

Etapa A: *terc*-butil-N^1(1,3-benzodioxol-5-ilmetil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

En un frasco de fondo redondo de 50 mL, Fmoc-1-Glu-(OtBu)-OH (2.127 g, 5 mmol) se disuelve en DMF (10 mL) y se agita a temperatura ambiente bajo nitrógeno. Se agrega PyBOP (2.6 g, 5 mmol) a la mezcla agitada seguido por piperonilamina (0.755 g, 5 mmol), y se agrega en forma de gota DIEA (1.2 equivalent). La mezcla se agita durante la noche (18-24 hr) a temperatura ambiente bajo nitrógeno. La mezcla de reacción

luego se vierte en 150 mL de agua y el sólido se recolecta y se lava con agua. El sólido húmedo luego se disuelve en acetato de etilo (ca. 500 mL), y se lava consecutivamente con 10% de HCl (aq.), $NaHCO_3$ (satur.), y NaCl (satur.). La fase orgánica se seca sobre $MgSO_4$ (anhi.) y se concentra. El producto crudo se redisuelve en acetona y se agregan hexanos. El sólido precipitado se filtra, se lava con hexanos y se seca en un secador de vacío durante la noche para dar 1.56 g de terc-butil N^1-(1,3-benzodioxol-5-ilmetil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato como sólido blanco fino. MS (ESI) m/z 559.1; HRMS: calculado para $C_{32}H_{34}N_2O_7$ + H+, 559.24388; encontrado (ESI_FT, $[M+H]^{1+}$), 559.24348.

Etapa B: terc-butil N^1-(1,3-benzodioxol-5-ilmetil)-L-α-glutaminato

El producto Fmoc-éster (1.5 g, 2.7 mmol) se disuelve (parcialmente) en acetonitrilo (17 mL) y se agita a temperatura ambiente bajo nitrógeno. La mezcla se disuelve completamente aproximadamente 30 min después de la adición de dietilamina (4.2 mL) y se agita durante dos horas. Después de terminar la reacción, la mezcla se concentra cuidadosamente (<30°C) bajo presión reducida mediante un evaporador rotatorio. El producto crudo (aceite claro) luego se filtra a través de una columna flash corta. La columna es gradiente eluida partiendo con 5% de Acetona/CH_2Cl_2 hasta que se remueve el subproducto Fmoc y se rampea a 50% de Acetona/CH_2Cl_2 mientras que se eluye el producto. Las fracciones deseadas se recolectan y se concentran dando 0.8 g

de aceite claro. MS (ESI) m/z 337.1; HRMS: calculado para $C_{17}H_{24}N_2O_5$ + H+, 337.17580; encontrado (ESI_FT, $[M+H]^{1+}$), 337.17605.

Etapa C: terc-butil N^1-(1,3-benzodioxol-5-ilmetil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutaminato

La amina libre (0.36 g, 1.07 mmol) se disuelve en DMF (5 mL) y se agita a ta bajo nitrógeno. Se agrega ácido 4-Bifenilcarboxílico (0.557 g, 1.07 mtnol) seguido por reactivo PyBOP (0.21 g, 1.07 mmol) con agitación vigorosa. La mezcla de reacción se enfría to 0°C y se agrega en forma de gota DIEA (1.2 equiv.). La reacción se completa en 14-24 hours. La mezcla de reacción luego se vierte en 100 mL agua y el sólido se recolecta. El sólido se redisuelve en acetato de etilo y se lava con 10% de HCl (aq.), $NaHCO_3$ (satur.), y NaCl (satur.). La fase orgánica se seca sobre Na_2SO_4 (anhi.) y se concentra. Se agrega scetona al residuo y se diluye con hexanos. El precipitado se recolecta y se seca en un secador de vacío durante la noche para dar 0.4 g del producto deseado. MS (ESI) m/z 517.2; HRMS: calculado para $C_{30}H_{32}N_2O_6$ + H+, 517.23331; encontrado (ESI_FT, $[M+H]^{1+}$), 517.23311.

Etapa D: N^1-(1,3-benzodioxol-5-ilmetil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

El t-butil éster (0.31 g, 0.6 mmol) se disuelve en CH_2Cl_2 (4 mL) y se agita a ta bajo nitrógeno. Se agrega ácido trifluoroacético (4 mL) disuelto en CH_2Cl_2 (4 mL) a la

solución y la solución amarilla clara se agita a ta durante 2 horas. La mezcla se evapora y se diluye tolueno (10 mL), se evapora completamente para remover el TFA. Un sólido se obtiene y se disuelve en un mínimo de acetona (ca. 25-50 mL) se calienta lentamente y se agrega hexanos. El sólido blanco se recolecta y se seca en un secador de vacío para producir 0.214 g del producto. MS (ESI) m/z 461.1; HRMS: calculado para $C_{26}H_{24}N_2O_6$ + H+, 461.17071; encontrado (ESI_FT, $[M+H]^{1+}$), 461.1704.

Ejemplo 8

Los siguientes compuestos se preparan de acuerdo con los procedimientos similares a aquellos del Ejemplo 7.

Ejemplo 8A: *N*^{2}-(*1,1*-bifenil-4-ilcarbonil)-*N*^{1}-ciclohexil-L-α-glutamina

Etapa A: *terc*-butil *N*^{1}-ciclohexil-*N*^{2}-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 507.2; HRMS: calculado para $C_{30}H_{38}N_2O_5$ + H+, 507.28535; encontrado (ESI_FT, PVM-H]$^{1+}$), 507.28583.

Etapa B: *terc*-butil N^1-ciclohexil-L-α-glutaminato

MS (ESI) *m/z* 285.2; HRMS: calculado para $C_{15}H_{28}N_2O_3$ + H+, 285.21727; encontrado (ESI_FT, [MH-H]$^{1+}$), 285.21644.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclohexil-L-α-glutaminato

MS (ESI) *m/z* 465.2; HRMS: calculado para $C_{28}H_{36}N_2O_4$ + H+, 465.27478; encontrado (ESI_FT, $[M+H]^{1+}$), 465.27386.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclohexil-L-α-glutamina

HRMS: calculado para $C_{24}H_{28}N_2O_4$ + H+, 409.21218; encontrado (ESI_FT, $[MH-H]^{1+}$), 409.21163.

Ejemplo 8B: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclopropil-L-α-glutamina

Etapa A: *terc*-butil N^1-ciclopropil-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 465.1; HRMS: calculado para $C_{27}H_{32}N_2O_5$ + H+, 465.23840; encontrado (ESI_FT, $[MH-H]^{1+}$), 465.23816.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclo*propil*-L-α-glutaminato

MS (ESI) *m/z* 423.2; HRMS: calculado para $C_{25}H_{30}N_2O_4$ + H+, 423.22783; encontrado (ESI_FT, $[MH-H]^{1+}$), 423.22725.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclopropil-L-α-glutamina

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MS (ESI) *m/z* 367.1; MS (ESI) *m/z* 1332; HRMS: calculado para $C_{2j}H_{22}N_2O_4$ + H+, 367.16523; encontrado (ESI_FT, $[MH-H]^{1+}$), 367.16454.

Ejemplo 8C: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-butil-L-α-glutamina

Etapa A: *terc*-butil N^1-butil-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 481.2; MS (ESI) *m/z* 503.2; HRMS: calculado para $C_{28}H_{36}N_2O_5$ + H+, 481.26970; encontrado (ESI_FT, $[MH-H]^{1+}$), 481.26789.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-butil-L-α-glutaminato

MS (ESI) *m/z* 439.1; MS (ESI) *m/z* 877.3; HRMS: calculado para $C_{26}H_{34}N_2O_4$ + H+, 439.25913; encontrado (ESI_FT, $[MH-H]^{1+}$), 439.25884.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-butil-L-α-glutamina

MS (ESI) *m/z* 381.2; MS (ESI) *m/z* 763.3; HRMS: calculado para $C_{22}H_{26}N_2O_4$ + H+, 383.19653; encontrado (ESI_FT, $[MH-H]^{1+}$), 383.19514.

Ejemplo 8D; N^2-(1,1'-bifenil-4-ilcarbonil)-A'^{r1}-(4-fluorobencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(4-fluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 533.2; HRMS: calculado para $C_{31}H_{33}FN_2O_5$ + H+, 533.24463; encontrado (ESI_FT, $[M+H]^{1+}$), 533.24546.

Etapa B: *terc*-butil N^1-(4-fluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 311.1; HRMS: calculado para $C_{16}H_{23}FN_2O_3$ + H+, 311.17655; encontrado (ESI_FT, $[M+H]^{1+}$), 311.17696.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 491.2; HRMS: calculado para $C_{29}H_{31}FN_2O_4$ + H+, 491.23406; encontrado (ESI_FT, $[M+H]^{1+}$), 491.23339.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fluorobencil)-L-α-glutamina

MS (ESI) *m/z* 435.1; HRMS: calculado para $C_{25}H_{23}FN_2O_4$ + H+, 435.17146; encontrado (ESI_FT, $[M+H]^{1+}$), 435.17056.

Ejemplo 8E: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclooctil-L-α-glutamina

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Etapa A: *terc*-butil N^1-ciclooctil-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 535.2; HRMS: calculado para $C_{32}H_{42}N_2O_5$ + H+, 535.31665; encontrado (ESI_FT, $[M+H]^{1+}$), 535.31782.

Etapa B: *terc*-butil N^1-ciclooctil-L-α-glutaminato

MS (ESI_FT) *m/z* 313.24821; MS (ESI_FT) *m/z* 313.24857; HRMS: calculado para $C_{17}H_{32}N_2O_3$ + H+, 313.24857; encontrado (ESI_FT, $[M+H]^{1+}$), 313.24821.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclooctil-L-α-glutaminato

MS (ESI) *m/z* 493.4; MS (ESI) *m/z* 985.6; HRMS: calculado para $C_{30}H_{40}N_2O_4$ + H+, 493.30608; encontrado (ESI_FTMS, $[M+H]^{1+}$), 493.30412.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N****ciclooctil-L-α-glutamina

MS (EST) *m/z* 437.3; MS (ESI) *m/z* 873.6; HRMS: calculado para $C_{26}H_{32}N_2O_4$ + H+, 437.24348; encontrado (ESI_FT, $[M+H]^{1+}$), 437.24272.

Ejemplo 8F: *N2*-(1,1'-bifenil-4-ilcarbonil)-*N1*-(3,4-dimetoxibencil)-L-α-glutamina

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Etapa A: *terc*-butil N^1-(3,4-dimetoxibencil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 575.3; MS (ESI) *m/z* 1149.6; HRMS: calculado para $C_{33}H_{38}N_2O_7$ + H+, 575.27518; encontrado (ESI_FT, $[M+H]^{1+}$), 575.27609.

Etapa B: *terc*-butil N^1-3,4-dimetoxibencil)-1-α-glutaminato

MS (ESI+) *m/z* 353.2; MS (ESI+) *m/z* 297.1; HRMS: calculado para $C_{18}H_{28}N_2O_5$ + H+, 353.20710; encontrado (ESI_FT, $[M+H]^{1+}$), 353.20629.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-dimetoxibencil)-L-α-glutaminato

MS (ESI+) *m/z* 533.3; HRMS: calculado para $C_{31}H_{36}N_2O_6$ + H+, 533.26461; encontrado (ESI_FT, $[M+H]^{1+}$), 533.26323.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-dimetoxibencil)-L-α-glutamina

MS (ESI-) *m/z* 475.3; HRMS: calculado para $C_{27}H_{28}N_2O_6$ + H+, 477.20201; encontrado (ESI_FT, $[M+H]^{1+}$), 477.20053.

Ejemplo 8G: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclopentil-L-α-glutamina

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Etapa A: *terc*-butil N^1-ciclopentil-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI+) *m/z* 493.3; MS (ESI+) *m/z* 437.2; HRMS: calculado para $C_{29}H_{36}N_2O_5$ + H+, 493.26970; encontrado (ESI_FT, $[M+H]^{1+}$), 493.26812.

Etapa B: *terc*-butil N^1-ciclopentil-L-α-glutaminato

MS (ESI) *m/z* 271.2; HRMS: calculado para $C_{14}H_{26}N_2O_3$ + H+, 271.20162; encontrado (ESI_FT, $[M+H]^{1+}$), 271.202.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclopentil-L-α-glutaminato

MS (ESI) *m/z* 451.3; MS (ESI) *m/z* 901.6; HRMS: calculado para $C_{27}H_{34}N_2O_4$ + H+, 451.25913; encontrado (ESI_FT, $[M+H]^{1+}$), 451.25803.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclopentil-L-α-glutamina

MS (ESI) *m/z* 395.2; MS (ESI) *m/z* 789.4; HRMS: calculado para $C_{23}H_{26}N_2O_4$ + H+, 395.19653; encontrado (ESI_FT, $[M+H]^{1+}$), 395.19564.

Ejemplo 8H: N^1-2-adamantil-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

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Etapa A: *terc*-butil N^1-2-adamantil-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 559.4; MS (ESI) *m/z* 1117.7; HRMS: calculado para $C_{34}H_{42}N_2O_5$ + H+, 559.31665; encontrado (ESI_FT, $[M+H]^{1+}$), 559.31524.

Etapa B: *terc*-butil N^1-2-adamantil-L-α-glutaminato

MS (ESI) *m/z* 337.2; MS (ESI) *m/z* 673.5; HRMS: calculado para $C_{19}H_{32}N_2O_3$ + H+, 337.24857; encontrado (ESI_FT, $[M+H]^{1+}$), 337.2475.

Etapa C: *terc*-butil N^1-2-adamantil-N^2-(1,1-bifenil-4-ilcarbonil)-L-α-glutaminato

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1033.6; HRMS: calculado para $C_{32}H_{40}N_2O_4$ + H+, 517.30608; encontrado (ESI_FT, $[M+H]^{1+}$), 517.30505.

Etapa D: N^1-2-adamantil-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 461.3; MS (ESI) *m/z* 921.5; HRMS: calculado para $C_{28}H_{32}N_2O_4$ + H+, 461.24348; encontrado (ESI_FT, $[M+H]^{1+}$), 461.24227.

Ejemplo 8I: N^1-(2-adamantilmetil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(2-adamantilmetil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 573.3; MS (ESI) *m/z* 1145.5; HRMS: calculado para $C_{35}H_{44}N_2O_5$ + H+, 573.33230; encontrado (ESI_FT, $[M+H]^{1+}$), 573.33089.

Etapa B: *terc*-butil N^1-(2-adamantilmetil)-L-α-glutaminato

MS (ESI) *m/z* 351.2; HRMS: calculado para $C_{20}H_{34}N_2O_3$ + H+, 351.26422; encontrado (ESI_FT, $[MH-H]^{1+}$), 351.26491.

Etapa C: *terc*-butil N^1-(2-adamantilmetil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutaminato

MS (ESI) *m/z* 531.3; MS (ESI) *m/z* 1061.4; HRMS: calculado para $C_{33}H_{42}N_2O_4$ + H+, 531.32173; encontrado (ESI__FT, $[M+H]^{1+}$), 531.32031.

Etapa D: N^1-(2-adamantilmetil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 475.2; MS (ESI) *m/z* 949.3; HRMS: calculado para $C_{29}H_{34}N_2O_4$ + H+, 475.25913; encontrado (ESI_FT, $[M+H]^{1+}$), 475.25734.

Ejemplo 8J: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metoxietil)-L-α-glutamina

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Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(2-metoxietil)-L-α-glutaminato

MS (ESI) *m/z* 483.2; MS (ESI) *m/z* 965.3; HRMS: calculado para $C_{27}H_{34}N_2O_6$ + H+, 483.24896; encontrado (ESI_FT, $[M+H]^{1+}$), 483.24851.

Etapa B: *terc*-butil N^1-(2-metoxietil)-L-α-glutaminato

MS (ESI) *m/z* 261.1; HRMS: calculado para $C_{12}H_{24}N_2O_4$ + H+, 261.18088; encontrado (ESI_FT, $[M+H]^{1+}$), 261.18071.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metoxietil)-L-α-glutaminato

MS (ESI) *m/z* 441.2; MS (ESI) *m/z* 881.3; HRMS: calculado para $C_{25}H_{32}N_2O_5$ + H+, 441.23840; encontrado (ESI_FT, $[M+H]^{1+}$), 441.23803.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metoxietil)-L-α-glutamina

MS (ESI) *m/z* 385.1; MS (ESI) *m/z* 769.2; HRMS: calculado para $C_{21}H_{24}N_2O_5$ + H+, 385.17580; encontrado (ESI_FT, $[M+H]^{1+}$), 385.17538.

Ejemplo 8K; N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metoxibencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(4-metoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 545.2; MS (ESI) *m/z* 1089.3; HRMS: calculado para $C_{32}H_{36}N_2O_6$ + H+, 545.26461; encontrado (ESI_FT, $[MH-H]^{1+}$), 545.26277.

Etapa B: *terc*-butil N^1-(4-metoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 323.2; HRMS: calculado para $C_{17}H_{26}N_2O_4$ + H+, 323.19653; encontrado (ESI_FT, $[M+H]^{1+}$), 323.19702.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metoxibencil)-L-α-glutaminato

MS (EST) *m/z* 503.2; MS (ESI) *m/z* 1005.4; HRMS: calculado para $C_{30}H_{34}N_2O_5$ + H+, 503.25405; encontrado (ESI_FT, $[M+H]^{1+}$), 503.25435.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metoxibencil)-L-α-glutamina

MS (ESI) *m/z* 445.2; MS (ESI) *m/z* 891.5; HRMS: calculado para $C_{26}H_{26}N_2O_5$ + H+, 447.19145; encontrado (ESI_FT, $[M+H]^{1+}$), 447.19235.

Ejemplo 8L: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3,4-dimetoxifenil)etil]-L-α-glutamina

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Etapa A: *terc*-butil N^1-[2-(3,4-dimetoxifenil)etil]-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 589.2; MS (ESI) *m/z* 1177.3; HRMS: calculado para $C_{34}H_{40}N_2O_7$ + H+, 589.29083; encontrado (ESI_FT, $[M+H]^{1+}$), 589.28932.

Etapa B: *terc*-butil N^1-[2-(3,4-dimetoxifenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 367.2; HRMS: calculado para $C_{19}H_{30}N_2O_5$ + H+, 367.22275; encontrado (ESI_FT, $[M+H]^{1+}$), 367.22308.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3,4-dimetoxifenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 547.3; MS (ESI) *m/z* 1093.4; HRMS: calculado para $C_{32}H_{38}N_2O_6$ + H+, 547.28026; encontrado (ESI_FT, $[M+H]^{1+}$), 547.280241.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3,4-dimetoxifenil)etil]-L-α-glutamina

MS (ESI) *m/z* 491.2; MS (ESI) *m/z* 981.2; HRMS: calculado para $C_{28}H_{30}N_2O_6$ + H+, 491.21766; encontrado (ESI_FT, $[M+H]^{1+}$), 491.21697.

Ejemplo 8M: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(4-metoxifenil)etil]-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[2-(4-metoxifenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 559.2; MS (ESI) *m/z* 1117.3; HRMS: calculado para $C_{33}H_{38}N_2O_6$ + H+, 559.28026; encontrado (ESI_FT, $[M+H]^{1+}$), 559.27899.

Etapa B: *terc*-butil N^1-[2-(4-metoxifenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 337.1; MS (ESI) *m/z* 673.3; HRMS: calculado para $C_{18}H_{28}N_2O_4$ + H+, 337.21218; encontrado (ESI_FT, $[M+H]^{1+}$), 337.21196.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(4-metoxifenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 517.2; MS (ESI) *m/z* 1033.4; HRMS: calculado para $C_{31}H_{36}N_2O_5$ + H+, 517.26970; encontrado (ESI_FT, $[M+H]^{1+}$), 517.26875.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(4-metoxifenil)etil]-L-α-glutamina

MS (ESI) *m/z* 461.2; MS (ESI) *m/z* 921.3; HRMS: calculado para $C_{27}H_{28}N_2O_5$ + H+, 461.20710; encontrado (ESI_FT, $[M+H]^{1+}$), 461.2062.

Ejemplo 8N: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(1-naftilmetil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(1- naftilmetil)-L-α-glutaminato

MS (ESI) *m/z* 565.2; MS (ESI) *m/z* 1129.4; HRMS: calculado para $C_{35}H_{36}N_2O_5$ + H+, 565.26970; encontrado (ESI_FT, $[M+H]^{1+}$), 565.26849.

Etapa B: *terc*-butil-N^1-(1-naftilmetil)-L-α-glutaminato

MS (ESI) *m/z* 343.1; MS (ESI) *m/z* 685.3; HRMS: calculado para $C_{20}H_{26}N_2O_3$ + H+, 343.20162; encontrado (ESI_FT, $[M+H]^{1+}$), 343.2014.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(1-naftilmetil)-L-α-glutaminato

MS (ESI) *m/z* 523.2; MS (ESI) *m/z* 1045.4; HRMS: calculado para $C_{33}H_{34}N_2O_4$ + H+, 523.25913; encontrado (ESI_FT, $[MH-H]^{1+}$), 523.2583.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(1-naftilmetil)-L-α-glutamina

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MS (ESI) *m/z* 467.2; MS (ESI) *m/z* 933.3; HRMS: calculado para $C_{29}H_{26}N_2O_4$ + H+, 467.19653; encontrado (ESI_FT, $[M+H]^{1+}$), 467.19528.

Ejemplo 80: N^2-(1,1'-bifenil-1-ilcarbonil)-N^1-(3-metilbencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(3- metilbencil)-L-α-glutaminato

MS (ESI) *m/z* 529.1; MS (ESI) *m/z* 1057.4; HRMS: calculado para $C_{32}H_{36}N_2O_5$ + H+, 529.26970; encontrado (ESI_FT, $[M+H]^{1+}$), 529.26804.

Etapa B: *terc*-butil N^1-(3-metilbencil)-L-α-glutaminato

MS (ESI) *m/z* 307.1; MS (ESI) *m/z* 613.3; HRMS: calculado para $C_{17}H_{26}N_2O_3$ + H+, 307.20162; encontrado (ESI_FT, $[MH-H]^{1+}$), 307.20079.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-metilbencil)-L-α-glutaminato

HRMS: calculado para $C_{30}H_{34}N_2O_4$ + H+, 487.25913; encontrado (ESI_FT, $[M+H]^{1+}$), 487.25842.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-metilbencil)-L-α-glutamina

HRMS: calculado para $C_{26}H_{26}N_2O_4$ + H+, 431.19653; encontrado (ESI_FT, $[M+H]^{1+}$), 431.19568.

Ejemplo 8P: N^2-(1,1'-bifenil-4-ilcarbonil)- N^1-(2-furilmetil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(2-furilmetil)-L-α-glutaminato

MS (ESI) *m/z* 505.2; HRMS: calculado para $C_{29}H_{32}N_2O_6$ + H+, 505.23331; encontrado (ESI_FT, $[M+H]^{1+}$), 505.23263.

Etapa B: *terc*-butil N^1-(2-furilmetil)-L-α-glutaminato

HRMS: calculado para $C_{14}H_{22}N_2O_4$ + H+, 283.16523; encontrado (ESI_FT, $[M+H]^{1+}$), 283.16497.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-furilmetil)-L-α-glutaminato

HRMS: calculado para $C_{27}H_{30}N_2O_5$ + H+, 463.22275; encontrado (ESI_FT, $[M+H]^{1+}$), 463.22212.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-furilmetil)-L-α-glutamina

HRMS: calculado para $C_{23}H_{22}N_2O_5$ + H+, 407.16015; encontrado (ESI_FT, $[MH-H]^{1+}$), 407.15957.

Ejemplo 8Q: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-metoxibencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(3- metoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 545.3; MS (ESI) *m/z* 1089.5; HRMS: calculado para $C_{32}H_{36}N_2O_6$ + H+, 545.26461; encontrado (ESI_FT, $[M+H]^{1+}$), 545.26286.

Etapa B: *terc*-butil N^1-(3-metoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 323.3; MS (ESI) *m/z* 645.7; HRMS: calculado para $C_{17}H_{26}N_2O_4$ + H+, 323.19653; encontrado (ESI_FT, $[M+H]^{1+}$), 323.19687.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-metoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 503.2; MS (ESI) *m/z* 1005.5; HRMS: calculado para $C_{30}H_{34}N_2O_5$ + H+, 503.25405; encontrado (ESI_FT, $[M+H]^{1+}$), 503.25322.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-metoxibencil)-L-α-glutamina

MS (ESI) *m/z* 447.2; MS (ESI) *m/z* 893.3; HRMS: calculado para $C_{26}H_{26}N_2O_5$ + H+, 447.19145; encontrado (ESI_FT, $[M+H]^{1+}$), 447.19079.

Ejemplo 8R: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(3,4,5-trimetoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 605.2; MS (ESI) *m/z* 1209 '.4; HRMS: calculado para $C_{34}H_{40}N_2O_8$ + H+, 605.28574; encontrado (ESI_FT, $[M+H]^{1+}$), 605.28453.

Etapa B: *terc*-butil N^1-(3,4,5-trimetoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 383.1; MS (ESI) *m/z* 765.3; HRMS: calculado para $C_{19}H_{30}N_2O_6$ + H+, 383.21766; encontrado (ESI_FT, $[M+H]^{1+}$), 383.21755.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 563.3; MS (ESI) *m/z* 1125.5; HRMS: calculado para $C_{32}H_{38}N_2O_7$ + H+, 563.27518; encontrado (ESI_FT, $[M+H]^{1+}$), 563.2744.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 507.2; MS (ESI) *m/z* 1013.4; HRMS: calculado para $C_{28}H_{30}N_2O_7$ + H+, 507.21258; encontrado (ESI_FT, $[M+H]^{1+}$), 507.21179.

Ejemplo 8S: N^2-(1,1^t-bifenil-4-ilcarbonil)-N^1-(2,4-diclorobencil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(2,4-diclorobencil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 583.1; HRMS: calculado para $C_{31}H_{32}Cl_2N_2O_5$ + H+, 583.17610; encontrado (ESL-FT, $[M+H]^{1+}$), 583.1742.

Etapa B: *terc*-butil N^1-(2,4-diclorobencil)-L-α-glutaminato

MS (ESI) *m/z* 361.1; MS (ESI) *m/z* 721.2; HRMS: calculado para $Ci_6H_{22}Cl_2N_2O_3$ + H+, 361.10802; encontrado (ESI_FT, $[M+H]^{1+}$), 361.10891.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,4-diclorobencil)-L-α-glutaminato

MS (ESI) *m/z* 541.2; MS (ESI) *m/z* 1081.3; HRMS: calculado para $C_{29}H_{30}Cl_2N_2O_4$ + H+, 541.16554; encontrado (ESI_FT, $[M+H]^{1+}$), 541.16693.

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Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,4-diclorobencil)-L-α-glutamina

MS (ESI) *m/z* 483.1; MS (ESI) *m/z* 967.2; HRMS: calculado para $C_{25}H_{22}Cl_2N_2O_4$ + H+, 485.10294; encontrado (ESI_FT, $[M+H]^{1+}$), 485.10231.

Ejemplo 8T: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-(trifluorometoxi)bencil]-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[4-(trifluorometoxi)bencil]-L-α-glutaminato

MS (ESI) *m/z* 599.1; MS (ESI) *m/z* 1197.3; HRMS: calculado para $C_{32}H_{33}F_3N_2O_6$ + H+, 599.23635; encontrado (ESI_FT, $[M+H]^{1+}$), 599.23521.

Etapa B: *terc*-butil N^1-[4-(trifluorometoxi)bencil)-L-α-glutaminato

MS (ESI) *m/z* 377.1; HRMS: calculado para $C_{17}H_{23}F_3N_2O_4$ + H+, 377.16827; encontrado (ESI_FT, $[M+H]^{1+}$), 377.16901.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-(trifluorometoxi)bencil]-L-α-glutaminato

MS (ESI) *m/z* 557.2; MS (ESI) *m/z* 1113.4; HRMS: calculado para $C_{30}H_{31}F_3N_2O_5$ + H+, 557.22578; encontrado (ESI_FT, $[M+H]^{1+}$), 557.22537.

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Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-(trifluorometoxi)bencil]-L-α-glutamina

MS (ESI) *m/z* 501.2; MS (ESI) *m/z* 1001.3; HRMS: calculado para $C_{26}H_{23}F_3N_2O_5$ + H+, 501.16318; encontrado (ESI_FT, $[M+H]^{1+}$), 501.16263.

Ejemplo 8U: N^2-(1,1'-bifenil-4-ilcarbonil-N^1-[3-(trifluorometoxilbencil]-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[3-(trifluorometoxi)bencil]-L-α-glutaminato

MS (ESI) *m/z* 599.2; MS (ESI) *m/z* 1197.4; HRMS: calculado para $C_{32}H_{33}F_3N_2O_6$ + H+, 599.23635; encontrado (ESI_FT, $[M+H]^{1+}$), 599.23596.

Etapa B: *terc*-butil N^1-[3-(trifluorometoxi)bencil]-L-α-glutaminato

MS (ESI) *m/z* 377.1; MS (ESI) *m/z* 753.3; HRMS: calculado para $C_{17}H_{23}F_3N_2O_4$ + H+, 377.16827; encontrado (ESI_FT, $[M+H]^{1+}$), 377.1691.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[3-(trifluorometoxi)bencil]-L-α-glutaminato

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MS (ESI) *m/z* 557.2; MS (ESI) *m/z* 1113.4; HRMS: calculado para $C_{30}H_{31}F_3N_2O_5$ + H+, 557.22578; encontrado (ESI_FT, $[M+H]^{1+}$), 557.22558.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[3-(trifluorometoxi)bencil]-L-α-glutamina

MS (ESI) *m/z* 499.1; MS (ESI) *m/z* 999.3; HRMS: calculado para $C_{26}H_{23}F_3N_2O_5$ + H+, 501.16318; encontrado (ESI_FT, $[M+H]^{1+}$), 501.16265.

Ejemplo 8V: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-fmetiltio)bencil]-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[4-(metiltio)bencil]-L-α-glutaminato

MS (ESI) *m/z* 561.2; MS (ESI) *m/z* 1121.4; HRMS: calculado para $C_{32}H_{36}N_2O_5S$ + H+, 561.24177; encontrado (ESI_FT, $[M+H]^{1+}$), 561.24183.

Etapa B: *terc*-butil N^1-[4-(metiltio)bencil]-L-α-glutaminato

MS (ESI) *m/z* 339.2; MS (ESI) *m/z* 677.3; HRMS: calculado para $C_{17}H_{26}N_2O_3S$ + H+, 339.17369; encontrado (ESI_FT, $[M+H]^{1+}$), 339.1748.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-(metiltio)bencil]-L-α-glutaminato

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MS (ESI) *m/z* 519.2; MS (ESI) *m/z* 1037.4; HRMS: calculado para $C_{30}H_{34}N_2O_4S$ + H+, 519.23120; encontrado (ESI_FT, $[M+H]^{1+}$), 519.23078.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-(metiltio)bencil]-L-α-glutamina

MS (ESI) *m/z* 461.1; MS (ESI) *m/z* 923.3; HRMS: calculado para $C_{26}H_{26}N_2O_4S$ + H+, 463.16860; encontrado (ESI_FT, $[MH-H]^{1+}$), 463.16807.

Ejemplo 8W: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fenoxibencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(4- fenoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 607.3; MS (ESI) *m/z* 1213.5; HRMS: calculado para $C_{37}H_{38}N_2O_6$ + H+, 607.28026; encontrado (ESI_FT, $[MH-H]^{1+}$), 607.27904.

Etapa B: *terc*-butil N^1-(4-fenoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 385.2; MS (ESI) *m/z* 769.4; HRMS: calculado para $C_{22}H_{28}N_2O_4$ + H+, 385.21218; encontrado (ESI_FT, $[MH-H]^{1+}$), 385.21141.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fenoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 565.3; MS (ESI) *m/z* 1129.5; HRMS: calculado para $C_{35}H_{36}N_2O_5$ + H+, 565.26970; encontrado (ESI_FT, $[MH-H]^{1+}$), 565.27062.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fenoxibencil)-L-α-glutamina

MS (ESI) *m/z* 507.2; MS (ESI) *m/z* 1015.4; HRMS: calculado para $C_{31}H_{28}N_2O_5$ + H+, 509.20710; encontrado (ESI_FT, $[MH-H]^{1+}$), 509.20657.

Ejemplo 8X: N^2-(1,1'-bifenil-4-ilcarbonil9-N^1-[2-(3-metoxifenil)etil]-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[2-(3-metoxifenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 559.3; MS (ESI) *m/z* 1117.6; HRMS: calculado para $C_{33}H_{38}N_2O_6$ + H+, 559.28026; encontrado (ESI_FT, $[MH-H]^{1+}$), 559.28074.

Etapa B: *terc*-butil N^1-[2-(3-metoxifenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 337.2; HRMS: calculado para $C_{18}H_{28}N_2O_4$ + H+, 337.21218; encontrado (ESI_FT, $[MH-H]^{1+}$), 337.21275.

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Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3-metoxifenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1033.6; HRMS: calculado para $C_{31}H_{36}N_2O_5$ + H+, 517.26970; encontrado (ESI_FT, $[M+H]^{1+}$), 517.27068.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3-metoxifenil)etil]-L-α-glutamina

MS (ESI) *m/z* 461.2; MS (ESI) *m/z* 921.4; HRMS: calculado para $C_{27}H_{28}N_2O_5$ + H+, 461.20710; encontrado (ESI_FT, $[MH-H]^{1+}$), 461.20723.

Ejemplo 8Y; N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,4-dimetoxibencil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(2,4-dimetoxibencil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 575.3; MS (ESI) *m/z* 1149.5; HRMS: calculado para $C_{33}H_{38}N_2O_7$ + H+, 575.27518; encontrado (ESI_FT, $[M+H]^{1+}$), 575.275181.

Etapa B: *terc*-butil N^1-(2,4-dimetoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 353.2; MS (ESI) *m/z* 705.4; HRMS: calculado para $C_{18}H_{28}N_2O_5$ + H+, 353.20710; encontrado (ESI_FT, $[M+H]^{1+}$), 353.20767.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,4-dimetoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 533.3; MS (ESI) *m/z* 1065.6; HRMS: calculado para $C_{31}H_{36}N_2O_6$ + H+, 533.26461; encontrado (ESI_FT, $[M+H]^{1+}$), 533.26569.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,4-dimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 477.2; MS (ESI) *m/z* 953.4; HRMS: calculado para $C_{27}H_{28}N_2O_6$ + H+, 477.20201; encontrado (ESI_FT, $[M+H]^{1+}$), 477.2019.

Ejemplo 8Z: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metoxibencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(2- metoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 545.2; HRMS: calculado para $C_{32}H_{36}N_2O_6$ + H+, 545.26461; encontrado (ESI_FT, $[M+H]^{1+}$), 545.26356.

Etapa B: *terc*-butil N^1-(2-metoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 323.2; MS (ESI) *m/z* 645.4; HRMS: calculado para $C_{17}H_{26}N_2O_4$ + H+, 323.19653; encontrado (ESI_FT, $[M+H]^{1+}$), 323.19657.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 503.2; MS (ESI) *m/z* 1005.5; HRMS: calculado para $C_{30}H_{34}N_2O_5$ + H+, 503.25405; encontrado (ESI_FT, $[MH-H]^{1+}$), 503.2546.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metoxibencil)-L-α-glutamina

MS (ESI) *m/z* 447.2; MS (ESI) *m/z* 893.4; HRMS: calculado para $C_{26}H_{26}N_2O_5$ + H+, 447.19145; encontrado (ESI_FT, $[M+H]^{1+}$), 447.19143.

Ejemplo 8AA: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,5-difluorobencil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(3,5-difluorobencil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 551.2; MS (ESI) *m/z* 1101.4; HRMS: calculado para $C_{31}H_{32}F_2N_2O_5$ + H+, 551.23521; encontrado (ESI_FT, $[MH-H]^{1+}$), 551.23338.

Etapa B: *terc*-butil N^1-(3,5-difluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 329.1; MS (ESI) *m/z* 657.3; HRMS: calculado para $C_{16}H_{22}F_2N_2O_3$ + H+, 329.16712; encontrado (ESI_FT, $[MH-H]^{1+}$), 329.16762.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,5-difluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 509.2; MS (ESI) *m/z* 1017.3; HRMS: calculado para $C_{29}H_{30}F_2N_2O_4$ + H+, 509.22464; encontrado (ESI_FTMS, $[MH-H]^{1+}$), 509.22463.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,5-difluorobencil)-L-α-glutamina

MS (ESI) *m/z* 451.1; MS (ESI) *m/z* 903.3; HRMS: calculado para $C_{25}H_{22}F_2N_2O_4$ + H+, 453.16204; encontrado (ESI_FTMS, $[MH-H]^{1+}$), 453.16222.

Ejemplo 8BB: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-diclorobencil)-L-α- glutamina

Etapa A: *terc*-butil N^1-(3,4-diclorobencil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 583.1; MS (ESI) *m/z* 1165.2; HRMS: calculado para $C_{31}H_{32}Cl_2N_2O_5$ + H+, 583.17610; encontrado (ESI_FT, $[M+H]^{1+}$), 583.17528.

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Etapa B: *terc*-butil N^1-(3,4-diclorobencil)-L-α-glutaminato

MS (ESI) *m/z* 361.1; MS (ESI) *m/z* 721.2; HRMS: calculado para $C_{16}H_{22}Cl_2N_2O_3$ + H+, 361.10802; encontrado (ESI_FT, $[M+H]^{1+}$), 361.10861.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-diclorobencil)-L-α-glutaminato

MS (ESI) *m/z* 541.2; MS (ESI) *m/z* 1081.3; HRMS: calculado para $C_{29}H_{30}Cl_2N_2O_4$ + H+, 541.16554; encontrado (ESI_FT, $[M+H]^{1+}$), 541.16685.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-diclorobencil)-L-α-glutamina

MS (ESI) *m/z* 483.1; MS (ESI) *m/z* 967.2; HRMS: calculado para $C_{25}H_{22}Cl_2N_2O_4$ + H+, 485.10294; encontrado (ESI_FTMS, $[M+H]^{1+}$), 485.10288.

Ejemplo 8CC; N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,5-dimetoxibencil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(3,5-dimetoxibencil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 575.3; HRMS: calculado para $C_{33}H_{38}N_2O_7$ + H+, 575.27518; encontrado (ESI_FTMS, $[M+H]^{1+}$), 575.27468.

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Etapa B: *terc*-butil N^1-(3,5-dimetoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 353.2; HRMS: calculado para $C_{18}H_{28}N_2O_5$ + H+, 353.20710; encontrado (ESI_FTMS, $[M+H]^{1+}$), 353.20732.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,5-dimetoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 533.3; MS (ESI) *m/z* 1065.5; HRMS: calculado para $C_{31}H_{36}N_2O_6$ + H+, 533.26461; encontrado (ESI_FTMS, $[M+H]^{1+}$), 533.26474.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,5-dimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 477.2; MS (ESI) *m/z* 953.4; HRMS: calculado para $C_{27}H_{28}N_2O_6$ + H+, 477.20201; encontrado (ESI-FTMS, $[M+H]^{1+}$), 477.202.

Ejemplo 8DD: N^2-(1,1'-bifenil-4-ilcarbonil)-N^4-(3,5-dimetilbencil)-L-α-glutamina

Etapa A: terc-butil N^1-(3,4-dimetilbencil)-N^1-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 543.3; MS (ESI) *m/z* 1085.4; HRMS: calculado para $C_{33}H_{38}N_2O_5$ + H+, 543.28535; encontrado (ESI_FTMS, $[M+H]^{1+}$), 543.28604.

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Etapa B: *terc*-butil N^1-(3,4-dimetilbencil)-L-α-glutaminato

MS (ESI) *m/z* 321.2; HRMS: calculado para $C_{18}H_{28}N_2O_3$ + H+, 321.21727; encontrado (ESI_FTMS, $[M-HH]^{1+}$), 321.21716.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-dimetilbencil)-L-α-glutaminato

MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.4; HRMS: calculado para $C_{31}H_{36}N_2O_4$ + H+, 501.27478; encontrado (ESI_FTMS, $[M+H]^{1+}$), 501.2735.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-dimetilbencil)-L-α-glutamina

MS (ESI) *m/z* 445.2; MS (ESI) *m/z* 889.3; HRMS: calculado para $C_{27}H_{28}N_2O_4$ + H+, 445.21218; encontrado (ESI_FTMS, $[M+H]^{1+}$), 445.21199.

Ejemplo 8EE; N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metilbencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(2-metilbencil)-L-α-glutaminato

MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.4; HRMS: calculado para $C_{32}H_{36}N_2O_5$ + H+, 529.26970; encontrado (ESI_FTMS, $[M+H]^{1+}$), 529.27003.

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Etapa B: *terc*-butil N^1-(2-metilbencil)-L-α-glutaminato

MS (ESI) *m/z* 307.2; MS (ESI) *m/z* 613.4; HRMS: calculado para $C_{17}H_{26}N_2O_3$ + H+, 307.20162; encontrado (ESI_FTMS, $[MH-H]^{1+}$), 307.20094.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metilbencil)-L-α-glutaminato

MS (ESI) *m/z* 487.2; MS (ESI) *m/z* 973.3; HRMS: calculado para $C_{30}H_{34}N_2O_4$ + H+, 487.25913; encontrado (ESI_FTMS, $[M+H]^{1+}$), 487.2588.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metilbencil)-L-α-glutamina

MS (ESI) *m/z* 431.2; MS (ESI) *m/z* 861.3; HRMS: calculado para $C_{26}H_{26}N_2O_4$ + H+, 431.19653; encontrado (ESI_FTMS, $[M-HH]^{1+}$), 431.1966.

Ejemplo 8FF: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(3-fenilpropil)-L-α-glutaminato

MS (ESI) *m/z* 543.3; HRMS: calculado para $C_{33}H_{38}N_2O_5$ + H+, 543.28535; encontrado (ESI_FTMS, $[M+H]^{1+}$), 543.2847.

Etapa B: *terc*-butil N^1-(3-fenilpropil)-1-α-glutaminato

MS (ESI) *m/z* 321.2; MS (ESI) *m/z* 641.4; HRMS: calculado para $C_{18}H_{28}N_2O_3$ + H+, 321.21727; encontrado (ESI_FTMS, $[M+H]^{1+}$), 321.2167.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutaminato

MS (ESI) *m/z* 501.3; HRMS: calculado para $C_{31}H_{36}N_2O_4$ + H+, 501.27478; encontrado (ESI_FTMS, $[M+H]^{1+}$), 501.2742.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutamina

MS (ESI) *m/z* 445.2; HRMS: calculado para $C_{27}H_{28}N_2O_4$ + H+, 445.21218; encontrado (ESI_FTMS, $[M+H]^{1+}$), 445.2121.

Ejemplo 8GG: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-2,3-dihidro-1*H*-inden-2-il-L-α-glutamina

Etapa A: *terc*-butil N^1-2,3-dihidro-1*H*-inden-2-il-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 541.2; MS (ESI) *m/z* 1081.4; HRMS: calculado para $C_{33}H_{36}N_2O_5$ + H+, 541.26970; encontrado (ESI-FTMS, $[M+H]^{1+}$), 541.27088.

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Etapa B: *terc*-butil N^1-2,3-dihidro-1*H*-inden-2-il-L-α-glutaminato

MS (ESI) *m/z* 319.1; MS (ESI) *m/z* 637.3; HRMS: calculado para $C_{18}H_{26}N_2O_3$ + H+, 319.20162; encontrado (ESI-FTMS, $[M+H]^{1+}$), 319.20275.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-2,3-dihidro-1*H*- inden-2-il-L-α-glutaminato

MS (ESI) *m/z* 499.2; MS (ESI) *m/z* 997.4; HRMS: calculado para $C_{31}H_{34}N_2O_4$ + H+, 499.25913; encontrado (ESI-FTMS, $[M+H]^{1+}$), 499.258.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-2,3-dihidro-1*H*-inden-2-il-L-α-glutamina

MS (ESI) *m/z* 441.2; MS (ESI) *m/z* 883.3; HRMS: calculado para $C_{27}H_{26}N_2O_4$ + H+, 443.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 443.19699.

Ejemplo 8HH: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,3-dimetilbencil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(2,3-dimetilbencil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

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MS (ESI) *m/z* 543.2; MS (ESI) *m/z* 1085.4; HRMS: calculado para $C_{33}H_{38}N_2O_5$ + H+, 543.28535; encontrado (ESI-FTMS, $[M+H]^{1+}$), 543.28623.

Etapa B: *terc*-butil N^1-(2,3-dimetilbencil)-L-α-glutaminato

MS (ESI) *m/z* 321.2; MS (ESI) *m/z* 641.4; HRMS: calculado para $C_{18}H_{28}N_2O_3$ + H+, 321.21727; encontrado (ESI-FTMS, $[M+H]^{1+}$), 321.2186.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,3-dimetilbencil)-L-α-glutaminato

MS (ESI) *m/z* 501.2; MS (ESI) *m/z* 1001.4; HRMS: calculado para $C_{31}H_{36}N_2O_4$ + H+, 501.27478; encontrado (ESI-FTMS, $[M+H]^{1+}$), 501.27629.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,3-dimetilbencil)-L-α-glutamina

MS (ESI) *m/z* 443.2; HRMS: calculado para $C_{27}H_{28}N_2O_4$ + H+, 445.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 445.21354.

Ejemplo 8II: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fenilbutil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(4-fenilbutil)-L-α-glutaminato

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MS (ESI) *m/z* 557.2; MS (ESI) *m/z* 1113.4; HRMS: calculado para $C_{34}H_{40}N_2O_5$ + H+, 557.30100; encontrado (ESI-FTMS, $[M+H]^{1+}$), 557.30162.

Etapa B: *terc*-butil N^1-(4-fenilbutil)-L-α-glutaminato

MS (ESI) *m/z* 335.2; HRMS: calculado para $C_{19}H_{30}N_2O_3$ + H+, 335.23292; encontrado (ESI-FTMS, $[M+H]^{1+}$), 335.23453;

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fenilbutil)-L-α-glutaminato

MS (ESI) *m/z* 515.3; MS (ESI) *m/z* 1029.5; HRMS: calculado para $C_{32}H_{38}N_2O_4$ + H+, 515.29043; encontrado (ESI-FTMS, $[M+H]^{1+}$), 515.29152.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fenilbutil)-L-α-glutamina

MS (ESI) *m/z* 459.2; MS (ESI) *m/z* 917.4; HRMS: calculado para $C_{28}H_{30}N_2O_4$ + H+, 459.22783; encontrado (ESI-FTMS, $[M+H]^{1+}$), 459.22972.

Ejemplo 8JJ: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-yodobencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(3- yodobencil)-L-α-glutaminato

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MS (ESI) *m/z* 641.1; MS (ESI) *m/z* 1281.1; HRMS: calculado para $C_{31}H_{33}IN_2O_5$ + H+, 641.15070; encontrado (ESI-FTMS, $[M+H]^{1+}$), 641.15111.

Etapa B: *terc*-butil N^1-(3-yodobencil)-L-α-glutaminato

MS (ESI) *m/z* 419.1; MS (ESI) *m/z* 837.1; HRMS: calculado para $C_{16}H_{23}IN_2O_3$ + H+, 419.08262; encontrado (ESI-FTMS, $[M+H]^{1+}$), 419.08459.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-yodobencil)-L-α-glutaminato

MS (ESI) *m/z* 599.1; MS (ESI) *m/z* 1197.1; HRMS: calculado para $C_{29}H_{31}IN_2O_4$ + H+, 599.14013; encontrado (ESI-FTMS, $[M+H]^{1+}$), 599.1414.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-yodobencil)-L-α-glutamina

MS (ESI) *m/z* 543.1; MS (ESI) *m/z* 1085.1; MS (ESI) *m/z* 601.1; HRMS: calculado para $C_{25}H_{23}IN_2O_4$ + H+, 543.07753; encontrado (ESI-FTMS, $[M+H]^{1+}$), 543.07723.

Ejemplo 8KK: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-*terc*-butilbencil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(4-*terc*-butilbencil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 571.3; MS (ESI) *m/z* 1141.6; HRMS: calculado para $C_{35}H_{42}N_2O_5$ + H+, 571.31665; encontrado (ESI_FT, $[M+H]^{1+}$), 571.31581.

Etapa B: *terc*-butil N^1-(4-*terc*-butilbencil)-L-α-glutaminato

MS (ESI) *m/z* 349.2; HRMS: calculado para $C_{20}H_{32}N_2O_3$ + H+, 349.24857; encontrado (ESI-FTMS, $[M+H]^{1+}$), 349.2489.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-*terc*-butilbencil)-L-α-glutaminato

MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.4; HRMS: calculado para $C_{33}H_{40}N_2O_4$ + H+, 529.30608; encontrado (ESI-FTMS, $[M+H]^{1+}$), 529.30622.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-*terc*-butilbencil)-L-α-glutamina

MS (ESI) *m/z* 473.2; MS (ESI) *m/z* 945.3; MS (ESI) *m/z* 531.2; HRMS: calculado para $C_{29}H_{32}N_2O_4$ + H+, 473.24348; encontrado (ESI-FTMS, $[M+H]^{1+}$), 473.24348.

Ejemplo 8LL: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-yodobencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(4- yodobencil)-L-α-glutaminato

MS (ESI) *m/z* 641.1; MS (ESI) *m/z* 1281.1; HRMS: calculado para $C_{31}H_{33}IN_2O_5$ + H+, 641.15070; encontrado (ESI-FTMS, $[M+H]^{1+}$), 641.15129.

Etapa B: *terc*-butil N^1-(4-yodobencil)-L-α-glutaminato

MS (ESI) *m/z* 419; HRMS: calculado para $C_{16}H_{23}IN_2O_3$ + H+, 419.08262; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 419.08332.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-yodobencil)-L-α-glutaminato

MS (ESI) *m/z* 599; MS (ESI) *m/z* 1197; HRMS: calculado para $C_{29}H_{31}IN_2O_4$ + H+, 599.14013; encontrado (ESI-FTMS, $[M+H]^{1+}$), 599.1407.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-yodobencil)-L-α-glutamina

MS (ESI) *m/z* 543; MS (ESI) *m/z* 1085; HRMS: calculado para $C_{25}H_{23}IN_2O_4$ + H+, 543.07753; encontrado (ESI-FTMS, $[M+H]^{1+}$), 543.07755.

Ejemplo 8MM: N^2-(bifenil-4-ilcarbonil)-N^1-(1,1'-dimetilpropil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(1,1'-dimetilpropil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

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MS (ESI) *m/z* 495.3; HRMS: calculado para $C_{29}H_{38}N_2O_5$ + H+, 495.28535; encontrado (ESI_FT, $[M+H]^{1+}$), 495.28577.

Etapa B: *terc*-butil N^1-(1,1'-dimetilpropyO-L-α-glutaminato

MS (ESI) *m/z* 273.2; HRMS: calculado para $C_{14}H_{28}N_2O_3$ + H+, 273.21727; encontrado (ESI-FTMS, $[M+H]^{1+}$), 273.21738.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(1,1-dimetilpropil)-L-α-glutaminato

MS (ESI) *m/z* 453.2; MS (ESI) *m/z* 905.5; HRMS: calculado para $C_{27}H_{36}N_2O_4$ + H+, 453.27478; encontrado (ESI-FTMS, $[M+H]^{1+}$), 453.27627.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(1,1-dimetilpropil)-L-α-glutamina

MS (ESI) *m/z* 397.2; MS (ESI) *m/z* 793.4; HRMS: calculado para $C_{23}H_{28}N_2O_4$ + H+, 397.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 397.2139.

Ejemplo 8NN: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

Etapa A: *terc*-butil N^1-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(9*H*- luoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 591.1; MS (ESI) *m/z* 1181.2; HRMS: calculado para $C_{34}H_{39}ClN_2O_5$ + H+, 591.26203; encontrado (ESI-FTMS, $[M+H]^{1+}$), 591.26263.

Etapa B: *terc*-butil N^1-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutaminato

MS (ESI) *m/z* 369.1; MS (ESI) *m/z* 737.2; HRMS: calculado para $C_{19}H_{29}ClN_2O_3$ + H+, 369.19395; encontrado (ESI-FTMS, $[M+H]^{1+}$), 369.19351.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutaminato

MS (ESI) *m/z* 549.1; MS (ESI) *m/z* 1097.2; RMS: calculado para $C_{32}H_{37}ClN_2O_4$ + H+, 549.25146; encontrado (ESI-FTMS, $[M+H]^{1+}$), 549.25189.

Etapa D: ^{2}-(bifenil-4-ilcarbonil)-N^1-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 493.1; HRMS: calculado para $C_{28}H_{29}ClN_2O_4$ + H+, 493.18886; encontrado (ESI- FTMS, $[M+H]^{1+}$), 493.1895.

Ejemplo 800: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletill-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutaminato

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MS (ESI) *m/z* 575.3; MS (ESI) *m/z* 1149.4; HRMS: calculado para $C_{34}H_{39}FN_2O_5$ + H+, 575.29158; encontrado (ESI-FTMS, $[M+H]^{1+}$), 575.29261.

Etapa B: *terc*-butil N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutaminato

MS (ESI) *m/z* 353.2; HRMS: calculado para $C_{19}H_{29}FN_2O_3$ + H+, 353.22350; encontrado (ESI-FTMS, $[M+H]^{1+}$), 353.22526.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutaminato

MS (ESI) *m/z* 533.2; MS (ESI) *m/z* 1065.4; HRMS: calculado para $C_{32}H_{37}FN_2O_4$ + H+, 533.28101; encontrado (ESI-FTMS, $[M+H]^{1+}$), 533.28063.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1- dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 477.2; MS (ESI) *m/z* 953.3; HRMS: calculado para $C_{28}H_{29}FN_2O_4$ + H+, 477.21841; encontrado (ESI-FTMS, $[M+H]^{1+}$), 477.21783.

Ejemplo 8PP: N^2-(bifenil-4-ilcarbonil)-N^1-(1,1-dimetil-2-feniletil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(1,1-dimetil-2-feniletil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 557.2; HRMS: calculado para $C_{34}H_{40}N_2O_5$ + H+, 557.30100; encontrado (ESI-FTMS, $[M+H]^{1+}$), 557.2994.

Etapa B: *terc*-butil N^1-(1,1-dimetil-2-feniletil)-L-α-glutaminato

MS (ESI) *m/z* 335.1; MS (ESI) *m/z* 669.3; HRMS: calculado para $C_{19}H_{30}N_2O_3$ + H+, 335.23292; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 335.23259.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(1,1-dimetil-2-feniletil)-L-α-glutaminato

MS (ESI) *m/z* 515.2; MS (ESI) *m/z* 1029.3; HRMS: calculado para $C_{32}H_{38}N_2O_4$ + H+, 515.29043; encontrado (ESI-FTMS, $[M+H]^{1+}$), 515.29018.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(isopropil)- glutamina

MS (ESI) *m/z* 459.1; MS (ESI) *m/z* 917.3; HRMS: calculado para $C_{28}H_{30}N_2O_4$ + H+, 459.22783; encontrado (ESI-FTMS, $[M+H]^{1+}$), 459.22858.

Ejemplo 8QQ: N^2-(bifenil-4-ilcarbonil)-N^1-(3-isopropoxipropil)-L-α-glutamina

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Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(3-isopropoxipropil)-L-α-glutaminato

MS (ESI) *m/z* 525.3; MS (ESI) *m/z* 1049.5; HRMS: calculado para $C_{30}H_{40}N_2O_6$ + H+, 525.29591; encontrado (ESI-FTMS, $[M+H]^{1+}$), 525.29528.

Etapa B: *terc*-butil N^1-(3-isopropoxiproil)-L-α-glutaminato

MS (ESI) *m/z* 303.2; HRMS: calculado para $C_{15}H_{30}N_2O_4$ + H+, 303.22783; encontrado (ESI-FTMS, $[M+H]^{1+}$), 303.22747.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(3-isopropoxipropil)-L-α-glutaminato

MS (ESI) *m/z* 483.3; MS (ESI) *m/z* 965.5; HRMS: calculado para $C_{28}H_{38}N_2O_5$ + H+, 483.28535; encontrado (ESI-FTMS, $[M+H]^{1+}$), 483.28364.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(3-isopropoxipropil)-L-α-glutamina

MS (ESI) *m/z* 427.2; MS (ESI) *m/z* 853.4; MS (ESI) *m/z* 449.2; HRMS: calculado para $C_{24}H_{30}N_2O_5$ + H+, 427.22275; encontrado (ESI-FTMS, $[M+H]^{1+}$), 427.22227.

Ejemplo 8RR: N^2-(bifenil-4-ilcarbonil)-N^1-(3-metilbutil)-L-α-glutamina

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Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(3-metilbutil)-L-α-glutaminato

MS (ESI) *m/z* 495.2; MS (ESI) *m/z* 989.5; HRMS: calculado para $C_{29}H_{38}N_2O_5$ + H+, 495.28535; encontrado (ESI-FTMS, $[M+H]^{1+}$), 495.28729.

Etapa B: *terc*-butil N^1-(3-metilbutil)-L-α-glutaminato

MS (ESI) *m/z* 273.2; HRMS: calculado para $C_{14}H_{28}N_2O_3$ + H+, 273.21727; encontrado (ESI-FTMS, $[M+H]^{1+}$), 273.21718.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(3-metilbutil)-L-α-glutaminato

MS (ESI) *m/z* 453.3; MS (ESI) *m/z* 905.5; MS (ESI) *m/z* 475.2; HRMS: calculado para $C_{27}H_{36}N_2O_4$ + H+, 453.27478; encontrado (ESI-FTMS, $[M+H]^{1+}$), 453.27427.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(3-metilbutil)-L-α-glutamina

MS (ESI) *m/z* 397.2; MS (ESI) *m/z* 793.3; HRMS: calculado para $C_{23}H_{28}N_2O_4$ + H+, 397.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 397.21129.

Ejemplo 8SS; -N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)etil]-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[2-(4-fluorofenil)etil]-L-α-glutaminato

MS (EST) *m/z* 547. ,2; MS (ESI) *m/z* 1093.3; HRMS: calculado para $C_{32}H_{35}FN_2O_5$ + H+, 547.26028; encontrado (ESI-FTMS, $[M+H]^{1+}$), 547.26067.

Etapa B: *terc*-butil N^1-[2-(4-fluorofenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 325.1; HRMS: calculado para $C_{17}H_{25}FN_2O_3$ + H+, 325.19220; encontrado (ESI-FTMS, $[M+H]^{1+}$), 325.19212.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 505.2; MS (ESI) *m/z* 1009.3; HRMS: calculado para $C_{30}H_{33}FN_2O_4$ + H+, 505.24971; encontrado (ESI-FTMS, $[M+H]^{1+}$), 505.25021.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)etil]-L-α-glutamina

MS (ESI) *m/z* 449.1; MS (ESI) *m/z* 897.2; HRMS: calculado para $C_{26}H_{25}FN_2O_4$ + H+, 449.18711; encontrado (ESI-FTMS, $[M+H]^{1+}$), 449.18705.

Ejemplo 8TT; N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-fluorofenil)etil]-L-α-glutamina

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Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[2-(2- fluorofenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 547.2; MS (ESI) *m/z* 1093.3; HRMS: calculado para $C_{32}H_{35}FN_2O_5$ + H+, 547.26028; encontrado (ESI-FTMS, $[M+H]^{1+}$), 547.26138.

Etapa B: *terc*-butil N^1-[2-(2-fluorofenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 325.1; MS (ESI) *m/z* 649.3; HRMS: calculado para $C_{17}H_{25}FN_2O_3$ + H+, 325.19220; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 325.19217.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-fluorofenil)etil]-L-α-glutaminato

MS (ESl) *m/z* 505.2; MS (ESI) *m/z* 1009.3; HRMS: calculado para $C_{30}H_{33}FN_2O_4$ + H+, 505.24971; encontrado (ESI-FTMS, $[M+H]^{1+}$), 505.2497.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-fluorofenil)etil]-L-α-glutamina

MS (ESI) *m/z* 449.1; MS (ESI) *m/z* 897.2; HRMS: calculado para $C_{26}H_{25}FN_2O_4$ + H+, 449.18711; encontrado (ESI-FTMS, $[M+H]^{1+}$), 449.18744.

Ejemplo 8UU: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-clorofenil)etil]-L-α-glutamina

Etapa A: *terc*-butil N^1-[2-(4-clorofenil)etil]-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 563.1; MS (ESI) *m/z* 1125.2; HRMS: calculado para $C_{32}H_{35}ClN_2O_5$ + Na+, 585.21267; encontrado (ESI-FTMS, $[M+Na]^{1+}$), 585.21454.

Etapa B: *terc*-butil N^1-[2-(4-clorofenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 341.1; MS (ESI) *m/z* 681.2; HRMS: calculado para $C_{17}H_{25}ClN_2O_3$ + H+, 341.16265; encontrado (ESI-FTMS, $[M+H]^{1+}$), 341.16311.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-clorofenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 521.2; MS (ESI) *m/z* 1041.3; HRMS: calculado para $C_{30}H_{33}ClN_2O_4$ + Na+, 543.20210; encontrado (ESI-FTMS, $[M+Na]^{1+}$), 543.20393.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-clorofenil)etil]-L-α-glutamina

MS (ESI) *m/z* 463.1; MS (ESI) *m/z* 927.1; HRMS: calculado para $C_{26}H_{25}ClN_2O_4$ + H+, 465.15756; encontrado (ESI-FTMS, $[M+H]^{1+}$), 465.15776.

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Ejemplo 8VV: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-clorofenil)etil]-L-α-glutamina

Etapa A: *terc*-butil N^1-[2-(2-clorofenil)etil]-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 563.1; MS (ESI) *m/z* 1125.2; HRMS: calculado para $C_{32}H_{35}ClN_2O_5$ + H+, 563.23073; encontrado (ESI-FTMS, $[M+H]^{1+}$), 563.23042.

Etapa B: *terc*-butil N^1-[2-(2-clorofenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 341.2; MS (ESI) *m/z* 681.3; MS (ESI) *m/z* 703.3; HRMS: calculado para $C_{17}H_{25}ClN_2O_3$ + H+, 341.16265; encontrado (ESI-FTMS, $[M+H]^{1+}$), 341.16301.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-clorofenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 521.2; MS (ESI) *m/z* 1041.4; HRMS: calculado para $C_{30}H_{33}ClN_2O_4$ + H+, 521.22016; encontrado (ESI-FTMS, $[M+H]^{1+}$), 521.22075.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-clorofenil)etil]-L-α- glutamina

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MS (ESI) *m/z* 465; MS (ESI) *m/z* 487; HRMS: calculado para $C_{26}H_{25}ClN_2O_4$ + H+, 465.15756; encontrado (ESI-FTMS, $[M+H]^{1+}$), 465.15834.

Ejemplo 8WW; N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-tienil)etil]-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[2-(2- tienil)etil]-L-α-glutaminato

MS (ESI) *m/z* 535.1; MS (ESI) *m/z* 1069.2; HRMS: calculado para $C_{30}H_{34}N_2O_5S$ + H+, 535.22612; encontrado (ESI-FTMS, $[M+H]^{1+}$), 535.22756.

Etapa B: *terc*-butil N^1-[2-(2-tienil)etil]-L-α-glutaminato

MS (ESI) *m/z* 313.1; MS (ESI) *m/z* 625.2; HRMS: calculado para $C_{15}H_{24}N_2O_3S$ + H+, 313.15804; encontrado (ESI-FTMS, $[M+H]^{1+}$), 313.15788.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-tienil)etil]-L-α-glutaminato

MS (ESI) *m/z* 493.2; MS (ESI) *m/z* 985.4; HRMS: calculado para $C_{28}H_{32}N_2O_4S$ + H+, 493.21555; encontrado (ESI-FTMS, $[M+H]^{1+}$), 493.21561.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-tienil)etil]-L-α-glutamina

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MS (ESI) *m/z* 437.1; MS (ESI) *m/z* 873.3; HRMS: calculado para $C_{24}H_{24}N_2O_4S$ + H+, 437.15295; encontrado (ESI-FTMS, $[M+H]^{1+}$), 437.15163.

Ejemplo 8XX; N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-fluorobencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(3-fluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 533.2; HRMS: calculado para $C_{31}H_{33}FN_2O_5$ + H+, 533.24463; encontrado (ESI_FTMS, $[M+H]^{1+}$), 533.2447.

Etapa B: *terc*-butil N^1-(3-fluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 311.2; HRMS: calculado para $C_{16}H_{23}FN_2O_3$ + H+, 311.17655; encontrado (ESI_FTMS, $[M+H]^{1+}$), 311.1764.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-fluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 491.2; MS (ESI) *m/z* 981.4; HRMS: calculado para $C_{29}H_{31}FN_2O_4$ + H+, 491.23406; encontrado (ESI_FTMS, $[M+H]^{1+}$), 491.2339.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-fluorobencil)-L-α-glutamina

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MS (ESI) *m/z* 435.1; MS (ESI) *m/z* 869.2; HRMS: calculado para $C_{25}H_{23}FN_2O_4$ + H+, 435.17146; encontrado (ESI_FTMS, $[MH-H]^{1+}$), 435.1712.

Ejemplo 8YY: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-clorofenil)etil]-L-α- glutamina

Etapa A: *terc*-butil N^1-[2-(3-clorofenil)etil]-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS *m/z* 03-305496LMS; HRMS: calculado para $C_{32}H_{35}ClN_2O_5$ + H+, 563.23073; encontrado (ESI_FTMS, $[M+H]^{1+}$), 563.2309.

Etapa B: *terc*-butil N^1-[2-(3-clorofenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 341.1; HRMS: calculado para $C_{17}H_{25}ClN_2O_3$ + H+, 341.16265; encontrado (ESLFTMS, $[M+H]^{1+}$), 341.1611.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3-clorofenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 521.1; MS (ESI) *m/z* 1041.1; HRMS: calculado para $C_{30}H_{33}ClN_2O_4$ + H+, 521.22016; encontrado (ESI-FTMS, $[M+H]^{1+}$), 521.22136.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3-clorofenil)etil]-L-α-glutamina

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MS (ESI-) *m/z* 463.2; MS (ESI-) *m/z* 197; HRMS: calculado para $C_{26}H_{25}ClN_2O_4$ + H+, 465.15756; encontrado (ESI-FTMS, $[M+H]^{1+}$), 465.15709.

Ejemplo 8ZZ: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-fluorobencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(2- fluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 533.1; MS (ESI) *m/z* 1065.1; HRMS: calculado para $C_{31}H_{33}FN_2O_5$ + H+, 533.24463; encontrado (ESI_FTMS, $[M+H]^{1+}$), 533.24461.

Etapa B: *terc*-butil N^1-(2-fluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 311.1; MS (ESI) *m/z* 621.2; HRMS: calculado para $C_{16}H_{23}FN_2O_3$ + H+, 311.17655; encontrado (ESI_FTMS, $[M+H]^{1+}$), 311.1762.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-fluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 491.1; MS (ESI) *m/z* 981.2; HRMS: calculado para $C_{29}H_{31}FN_2O_4$ + H+, 491.23406; encontrado (ESI-FTMS, $[M+H]^{1+}$), 491.23526.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-fluorobencil)-L-α-glutamina

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MS (ESI-) *m/z* 433.1; HRMS: calculado para $C_{25}H_{23}FN_2O_4$ + H+, 435.17146; encontrado (ESI-FTMS, $[M+H]^{1+}$), 435.17161.

Ejemplo 8AAA: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-difluorobencil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(3,4-difluorobencil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 551.2; MS (ESI) *m/z* 1101.4; HRMS: calculado para $C_{31}H_{32}F_2N_2O_5$ + H+, 551.23521; encontrado (ESI_FT, $[M+H]^{1+}$), 551.23407.

Etapa B: *terc*-butil N^1-(3,4-difluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 329; MS (ESI) *m/z* 657.2; HRMS: calculado para $C_{16}H_{22}F_2N_2O_3$ + H+, 329.16712; encontrado (ESI_FTMS, $[M+H]^{1+}$), 329.1664.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-difluorobencil)-L-α-glutaminato

MS (ESI) *m/z* 509.1; MS (ESI) *m/z* 1017.1; HRMS: calculado para $C_{29}H_{30}F_2N_2O_4$ + H+, 509.22464; encontrado (ESI-FTMS, $[M+H]^{1+}$), 509.22485.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-difluorobencil)-L-α-glutamina

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MS (ESI-) *m/z* 451.1; HRMS: calculado para $C_{25}H_{22}F_2N_2O_4$ + H+, 453.16204; encontrado (ESI-

FTMS, $[M+H]^{1+}$), 453.1614.

Ejemplo 8BBB: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(sec-butil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(sec-butil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 481.2; HRMS: calculado para $C_{28}H_{36}N_2O_5$ + H+, 481.26970; encontrado (ESI-FTMS, $[M+H]^{1+}$), 481.26966.

Etapa B: *terc*-butil N^1-(sec-butil)-L-α-glutaminato

MS (ESI) *m/z* 259.1; HRMS: calculado para $C_{13}H_{26}N_2O_3$ + H+, 259.20162; encontrado (ESI-FTMS, $[M+H]^{1+}$), 259.20164.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(sec-butil)-L-α-glutaminato

MS (ESI) *m/z* 439.2; MS (ESI) *m/z* 877.4; HRMS: calculado para $C_{26}H_{34}N_2O_4$ + H+, 439.25913; encontrado (ESI-FTMS, $[M+H]^{1+}$), 439.25972.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(sec-butil)-L-α-glutamina

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MS (ESI) *m/z* 383.1; MS (ESI) *m/z* 765.3; MS (ESI) *m/z* 441.2; HRMS: calculado para $C_{22}H_{26}N_2O_4$ + H+, 383.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 383.19745.

Ejemplo 8CCC: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(ciclopropilmetil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(ciclopropilmetil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 479.2; MS (ESI) *m/z* 957.3; HRMS: calculado para $C_{28}H_{34}N_2O_5$ + H+, 479.25405; encontrado (ESI-FTMS, $[M+H]^{1+}$), 479.25563.

Etapa B: *terc*-butil N^1-(ciclopropilmetil)-L-α-glutaminato

MS (ESI) *m/z* 257.1; HRMS: calculado para $C_{13}H_{24}N_2O_3$ + H+, 257.18597; encontrado (ESI-FTMS, $[M+H]^{1+}$), 257.18608.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(ciclopropilmetil)-L-α-glutaminato

MS (ESI) *m/z* 437.2; MS (ESI) *m/z* 873.3; HRMS: calculado para $C_{26}H_{32}N_2O_4$ + H+, 437.24348; encontrado (ESI-FTMS, $[M+H]^{1+}$), 437.24446.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(ciclopropilmetil)-L-α-glutamina

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MS (ESI) *m/z* 381.1; MS (ESI) *m/z* 761.2; HRMS: calculado para $C_{22}H_{24}N_2O_4$ + H+, 381.18088; encontrado (ESI-FTMS, $[M+H]^{1+}$), 381.18186.

Ejemplo 8DDD: N^2-(bifenil-4-ilcarbonil)-N^1-(2-morfolin-4-iletil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(2-morfolin-4-iletil)-L-α-glutaminato

MS (ESI) *m/z* 538.3; HRMS: calculado para $C_{30}H_{39}N_3O_6$ + H+, 538.29116; encontrado (ESI-FTMS, $[M+H]^{1+}$), 538.29233.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(2-morfolin-4-iletil)-L-α-glutaminato

MS (ESI) *m/z* 496.2; HRMS: calculado para $C_{28}H_{37}N_3O_5$ + H+, 496.28060; encontrado (ESI-FTMS, $[M+H]^{1+}$), 496.28079.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(2-morfolin-4-iletil)-L-α-glutamina

MS (ESI) *m/z* 440.2; HRMS: calculado para $C_{24}H_{29}N_3O_5$ + H+, 440.21800; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 440.21827.

Ejemplo 8EEE: N^2-(bifenil-4-ilcarbonil)-N^1,N^1-dietil-L-α-glutamina

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Etapa A: *terc*-butil N^1,N^1-dietil-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 481.3; MS (ESI) *m/z* 961.5; HRMS: calculado para $C_{28}H_{36}N_2O_5$ + Na+, 503.25164; encontrado (ESI-FTMS, $[M+Na]^{1+}$), 503.25163.

Etapa B: *terc*-butil N^1,N^1-dietil-L-α-glutaminato

MS (ESI) *m/z* 259.2; HRMS: calculado para $C_{13}H_{26}N_2O_3$ + H+, 259.20162; encontrado (ESI-FTMS, $[M+H]^{1+}$), 259.20149.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1,N^1-dietil-L-α-glutaminato

MS (ESI) *m/z* 439.2; MS (ESI) *m/z* 877.4; HRMS: calculado para $C_{26}H_{34}N_2O_4$ + H+, 439.25913; encontrado (ESI-FTMS, $[M+H]^{1+}$), 439.26093.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1,N^1-dietil-L-α-glutamina

MS (ESI) *m/z* 383.2; MS (ESI) *m/z* 765.4; HRMS: calculado para $C_{22}H_{26}N_2O_4$ + H+, 383.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 383.19675.

Ejemplo 8FFF: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-feniletil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(2- feniletil)-L-α-glutaminato

MS (ESI) *m/z* 529.2; HRMS: calculado para $C_{32}H_{36}N_2O_5$ + H+, 529.26970; encontrado (ESI_FTMS, $[M+H]^{1+}$), 529.2693.

Etapa B: *terc*-butil N^1-(2-feniletil)-L-α-glutaminato

HRMS: calculado para $C_{17}H_{26}N_2O_3$ + H+, 307.20162; encontrado (ESI_FTMS, $[M+H]^{1+}$), 307.2011.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-feniletil)-L-α-glutaminato

MS (ESI) *m/z* 487.2; MS (ESI) *m/z* 973.3; HRMS: calculado para $C_{30}H_{34}N_2O_4$ + H+, 487.25913; encontrado (ESI_FTMS, $[M+H]^{1+}$), 487.2588.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 431.2; MS (ESI) *m/z* 861.3; HRMS: calculado para $C_{26}H_{26}N_2O_4$ + H+, 431.19653; encontrado (ESI_FTMS, $[M+H]^{1+}$), 431.1963.

Ejemplo 8GGG: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[3-(trifluorometil)bencill-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[3-(trifluorometil)bencil]-L-α-glutaminato

MS (ESI) *m/z* 583.2; HRMS: calculado para $C_{32}H_{33}F_3N_2O_5$ + H+, 583.24143; encontrado (ESLFTMS, $[M+H]^{1+}$), 583.2409.

Etapa B: *terc*-butil N^1-[3-(trifluorometil)bencil]-L-α-glutaminato

HRMS: calculado para $C_{17}H_{23}F_3N_2O_3$ + H+, 361.17335; encontrado (ESI_FTMS, $[M+H]^{1+}$), 361.173.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil-N^1-[3-(trifluorometil)bencil]-L-α-glutaminato

MS (ESI) *m/z* 541.2; MS (ESI) *m/z* 1081.3; HRMS: calculado para $C_{30}H_{31}F_3N_2O_4$ + H+, 541.23087; encontrado (ESI_FTMS, $[M+H]^{1+}$), 541.2301.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[3-(trifluorometil)bencil]-L-α-glutamina

MS (ESl) *m/z* 485.2; MS (ESI) *m/z* 969.3; HRMS: calculado para $C_{26}H_{23}F_3N_2O_4$ + H+, 485.16827; encontrado (ESI_FTMS, $[MH-H]^{1+}$), 485.1682.

Ejemplo 8HHH; N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-[trifluorometil)bencil]-1-α-glutamina

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Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[2-(trifluorometil)bencil]-L-α-glutaminato

MS (ESI) *m/z* 583.2; HRMS: calculado para $C_{32}H_{33}F_3N_2O_5$ + H+, 583.24143; encontrado (ESI_FT, $[M+H]^{1+}$), 583.24162.

Etapa B: *terc*-butil N^1-[2-(trifluorometil)bencil]-L-α-glutaminato

HRMS: calculado para $C_{17}H_{23}F_3N_2O_3$ + H+, 361.17335; encontrado (ESI_FTMS, $[M+H]^{1+}$), 361.1725.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(trifluorometil)bencil]-L-α-glutaminato

MS (ESI) *m/z* 541.2; MS (ESI) *m/z* 1081.2; HRMS: calculado para $C_{30}H_{31}F_3N_2O_4$ + H+, 541.23087; encontrado (ESI_FTMS, $[M+H]^{1+}$), 541.23091.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(trifluorometil)bencil]-L-α-glutamina

MS (ESI) *m/z* 485; MS (ESI) *m/z* 969; HRMS: calculado para $C_{26}H_{23}F_3N_2O_4$ + H+, 485.16827; encontrado (ESI_FTMS, $[MH-H]^{1+}$), 485.168.

Ejemplo 8III: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metilbencil)-L-α-glutamina

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Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(4- metilbencil)-L-α-glutaminato

MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.4; HRMS: calculado para $C_{32}H_{36}N_2O_5$ + H+, 529.26970; encontrado (ESI_FT, $[M+H]^{1+}$), 529.26796.

Etapa B: *terc*-butil N^1-(4-metilbencil)-L-α-glutaminato

HRMS: calculado para $C_{17}H_{26}N_2O_3$ + H+, 307.20162; encontrado (ESI-FTMS, $[M+H]^{1+}$), 307.20274.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metilbencil)-L-α-glutaminato

HRMS: calculado para $C_{30}H_{34}N_2O_4$ + H+, 487.25913; encontrado (ESI-FTMS, $[M+H]^{1+}$), 487.25856.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metilbencil)-L-α-glutamina

HRMS: calculado para $C_{26}H_{26}N_2O_4$ + H+, 431.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 431.19627.

Ejemplo 8JJJ: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-heptil-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-heptil-L-α-glutaminato

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MS (ESI) *m/z* 523.3; MS (ESI) *m/z* 1045.5; HRMS: calculado para $C_{31}H_{42}N_2O_5$ + H+, 523.31665; encontrado (ESI-FTMS, $[M+H]^{1+}$), 523.31783.

Etapa B: *terc*-butil N^1-heptil-L-α-glutaminato

HRMS: calculado para $C_{16}H_{32}N_2O_3$ + H+, 301.24857; encontrado (ESI-FTMS, $[M+H]^{1+}$), 301.2499.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-heptil-L-α-glutaminato

HRMS: calculado para $C_{29}H_{40}N_2O_4$ + H+, 481.30608; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 481.30706.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-heptil-L-α-glutamina

HRMS: calculado para $C_{25}H_{32}N_2O_4$ + H+, 425.24348; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 425.24417.

Ejemplo 8KKK: N^3-(bifenil-4-ilcarbonil)-N^1-[2-(4-bromofenil)etil]-L-α-glutamina

Etapa A: *terc*-butil N^1-[2-(4-bromofenil)etil]-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

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MS (ESI) *m/z* 607.1; HRMS: calculado para $C_{32}H_{35}BrN_2O_5$ + H+, 607.18021; encontrado (ESI-FTMS, $[M+H]^{1+}$), 607.18182.

Etapa B: *terc*-butil N^1-[2-(4-bromofenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 385; HRMS: calculado para $C_{17}H_{25}BrN_2O_3$ + H+, 385.11213; encontrado (ESI-FTMS, $[M+H]^{1+}$), 385.11309.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-bromofenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 565.1; MS (ESI) *m/z* 1129.1; HRMS: calculado para $C_{30}H_{33}BrN_2O_4$ + H+, 565.16965; encontrado (ESI-FTMS, $[M+H]^{1+}$), 565.17.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-bromofenil)etil]-L-α-glutamina

MS (ESI) *m/z* 507.2; HRMS: calculado para $C_{26}H_{25}BrN_2O_4$ + H+, 509.10705; encontrado (ESI-FTMS, $[M+H]^{1+}$), 509.10906.

Ejemplo 8LLL: N^2-(bifenil-4-ilcarbonil-N^1-(3,3-dimetilbutil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(3,3-dimetilbutil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

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MS (ESI) *m/z* 509.3; MS (ESI) *m/z* 1017.5; HRMS: calculado para $C_{30}H_{40}N_2O_5$ + H+, 509.30100; encontrado (ESI-FTMS, $[M+H]^{1+}$), 509.30165.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(3,3-dimetilbutil)-L-α-glutaminato

MS (ESI) *m/z* 467.3; MS (ESI) *m/z* 933.5; MS (ESI) *m/z* 489.3; HRMS: calculado para $C_{28}H_{38}N_2O_4$ + H+, 467.29043; encontrado (ESI-FTMS, $[M+H]^{1+}$), 467.29134.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(3,3-dimetilbutil)-L-α-glutamina

HRMS: calculado para $C_{24}H_{30}N_2O_4$ + H+, 411.22783; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 411.22929.

Ejemplo 8MMM: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(3-bromofenil)etil]-L-α-glutamina

Etapa A: *terc*-butil N^1-[2-(3-bromofenil)etil]-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 607.1; MS (ESI) *m/z* 1213.3; HRMS: calculado para $C_{32}H_{35}BrN_2O_5$ + H+, 607.18021; encontrado (ESI-FTMS, $[M+H]^{1+}$), 607.18017.

Etapa B: *terc*-butil N^1-[2-(3-bromofenil)etil]-L-α-glutaminato

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MS (ESI) *m/z* 385.1; MS (ESI) *m/z* 769.2; HRMS: calculado para $C_{17}H_{25}BrN_2O_3$ + H+, 385.11213; encontrado (ESI-FTMS, $[M+H]^{1+}$), 385.11175.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(3-bromofenil)etil]-L-α-glutaminato

HRMS: calculado para $C_{30}H_{33}BrN_2O_4$ + H+, 565.16965; encontrado (ESI-FTMS, $[M+H]^{1+}$), 565.16854.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(3-bromofenil)etil]-L-α-glutamina

HRMS: calculado para $C_{26}H_{25}BrN_2O_4$ + H+, 509.10705; encontrado (ESI-FTMS, $[M+H]^{1+}$), 509.10648.

Ejemplo 8NNN: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-fluoro-3-(trifluorometil)bencil]-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[4-fluoro-3-(trifluorometil)bencil]-L-α-glutaminato

MS (ESI) *m/z* 601.2; MS (ESI) *m/z* 1201.3; HRMS: calculado para $C_{32}H_{32}F_4N_2O_5$ + H+, 601.23201; encontrado (ESI-FTMS, $[M+H]^{1+}$), 601.23172.

Etapa B: *terc*-butil N^1-[4-fluoro-3-(trifluorometil)bencil]-L-α-glutaminato

472

HRMS: calculado para $C_{17}H_{22}F_4N_2O_3$ + H+, 379.16393; encontrado (ESI-FTMS, $[M+H]^{1+}$), 379.16566.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-fluoro-3-(trifluorometil)bencil]-L-α-glutaminato

HRMS: calculado para $C_{30}H_{30}F_4N_2O_4$ + H+, 559.22145; encontrado (ESI-FTMS, $[M+H]^{1+}$), 559.22077.

Etapa D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-fluoro-3-(trifluorometil)bencil]-L-α-glutamina

HRMS: calculado para $C_{26}H_{22}F_4N_2O_4$ + H+, 503.15885; encontrado (ESI-FTMS, $[M+H]^{1+}$), 503.1582.

Ejemplo 8000: N^2-(bifenil-4-ilcarbonil)-N^1-(3,3-difenilpropil)-L-α-glutamina

Etapa A: *terc*-butil N^1-(3,3-difenilpropil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 619.3; MS (ESI) *m/z* 1237.6; HRMS: calculado para $C_{39}H_{42}N_2O_5$ + H+, 619.31665; encontrado (ESI-FTMS, $[M+H]^{1+}$), 619.31658.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(3,3-difenilpropil)-L-α-glutaminato

473

HRMS: calculado para $C_{37}H_{40}N_2O_4$ + H+, 577.30608; encontrado (ESI-FTMS, $[M+H]^{1+}$), 577.30483.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(3,3-difenilpropil)-L-α-glutamina

HRMS: calculado para $C_{33}H_{32}N_2O_4$ + H+, 521.24348; encontrado (ESI-FTMS, $[M+H]^{1+}$), 521.24166.

Ejemplo 8PPP: N^2-(bifenil-4-ilcarbonil)-N^1-isopropil-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-isopropil-L-α-glutaminato

MS (ESI) *m/z* 467.2; MS (ESI) *m/z* 933.5; HRMS: calculado para $C_{27}H_{34}N_2O_5$ + Na+, 489.23599; encontrado (ESI-FTMS, $[M+Na]^{1+}$), 489.23577.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-isopropil-L-α-glutaminato

MS (ESI) *m/z* 425.2; MS (ESI) *m/z* 441.2; MS (ESI) *m/z* 871.4; HRMS: calculado para $C_{25}H_{32}N_2O_4$ + Na+, 447.22543; encontrado (ESI-FTMS, $[M+Na]^{1+}$), 447.22701.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-isopropil-L-α-glutamina

474

MS (ESI) *m/z* 367.2; MS (ESI) *m/z* 735.3; MS (ESI) *m/z* 481.2; HRMS: calculado para $C_{21}H_{24}N_2O_4$ + Na+, 391.16283; encontrado (ESI-FTMS, $[M+Na]^{1+}$), 391.16451.

Ejemplo 8QQQ: N^2-(bifenil-4-ilcarbonil)-N^1-(piridin-4-ilmetil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(piridin-4-ilmetil)-L-α-glutaminato

MS (ESI) *m/z* 516.3; HRMS: calculado para $C_{30}H_{33}N_3O_5$ + H+, 516.24930; encontrado (ESI_ FTMS, $[M+H]^{1+}$), 516.24875.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(piridin-4-ilmetil)-L-α-glutaminato

MS (ESl) *m/z* 474.2; HRMS: calculado para $C_{28}H_{31}N_3O_4$ + H+, 474.23873; encontrado (ESI- FTMS, $[M+H]^{1+}$), 474.24265.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(piridin-4-ilmetil)-L-α-glutamina

HRMS: calculado para $C_{24}H_{23}N_3O_4$ + H+, 418.17613; encontrado (ESI-FTMS, $[M+H]^{1+}$), 418.17812.

Ejemplo 8RRR: N^2-(bifenil-4-ilcarbonil)-N^1-pentil-L-α-glutamina

475

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-pentil-L-α-glutaminato

MS (ESI) *m/z* 495.2; MS (ESI) *m/z* 989.5; HRMS: calculado para $C_{29}H_{38}N_2O_5$ + Na+, 517.26729; encontrado (ESI-FTMS, $[M+Na]^{1+}$), 517.26785.

Etapa B: *terc*-butil N^1-pentil-L-α-glutaminato

MS (ESI) *m/z* 273.2; HRMS: calculado para $C_{14}H_{28}N_2O_3$ + H+, 273.21727; encontrado (ESI- FTMS, $[M+H]^{1+}$), 273.21761.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-pentil-L-α-glutaminato

MS (ESI) *m/z* 453.2; MS (ESI) *m/z* 905.5; HRMS: calculado para $C_{27}H_{36}N_2O_4$ + H+, 453.27478; encontrado (ESI-FTMS, $[M+H]^{1+}$), 453.27694.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-pentil-L-α-glutamina

MS (ESI) *m/z* 397.2; MS (ESI) *m/z* 793.4; HRMS: calculado para $C_{23}H_{28}N_2O_4$ + H+, 397.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 397.2136.

Ejemplo 8SSS: N^2-(bifenil-4-ilcarbonil)-N^1-(*terc*-butil)-L-α-glutamina

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Etapa A: *terc*-butil N^1-(*terc*-butil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 481.2; MS (ESI) *m/z* 961.5; HRMS: calculado para $C_{28}H_{36}N_2O_5$ + H+, 481.26970; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 481.27074.

Etapa B: *terc*-butil N^1-(*terc*-butil)-L-α-glutaminato

MS (ESI) *m/z* 259.1; MS (ESI) *m/z* 517.3; HRMS: calculado para $C_{13}H_{26}N_2O_3$ + H+, 259.20162; encontrado (ESI-FTMS, $[M+H]^{1+}$), 259.20174.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(*terc*-butil)-L-α-glutaminato

MS (ESI) *m/z* 439.2; MS (ESI) *m/z* 877.4; HRMS: calculado para $C_{26}H_{34}N_2O_4$ + H+, 439.25913; encontrado (ESI-FTMS, $[M+H]^{1+}$), 439.25922.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(*terc*-butil)-L-α-glutamina

MS (ESI) *m/z* 383.2; MS (ESI) *m/z* 765.3; HRMS: calculado para $C_{22}H_{26}N_2O_4$ + H+, 383.19653; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 383.19812.

Ejemplo 8TTT: N^2-(bifenil-4-ilcarbonil)-N^1-(1-metil-1-feniletil)-L-α-glutamina

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Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(1-metil-1-feniletil)-L-α-glutaminato

MS (ESI) *m/z* 543.2; MS (ESI) *m/z* 1085.4; HRMS: calculado para $C_{33}H_{38}N_2O_5$ + H+, 543.28535; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 543.28707.

Etapa B: *terc*-butil N^1-(1-metil-1-feniletil)-L-α-glutaminato

MS (ESI) *m/z* 321.1; MS (ESI) *m/z* 641.3; HRMS: calculado para $C_{18}H_{28}N_2O_3$ + H+, 321.21727; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 321.21716.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(1-metil-1-feniletil)-L-α-glutaminato

MS (ESI) *m/z* 501.2; MS (ESI) *m/z* 1001.4; HRMS: calculado para $C_{31}H_{36}N_2O_4$ + H+, 501.27478; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 501.27462.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(1-metil-1-feniletil)-L-α-glutamina

HRMS: calculado para $C_{27}H_{28}N_2O_4$ + H+, 445.21218; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 445.21311.

Ejemplo 8UUU: N^2-(bifenil-4-ilcarbonil)-N^1-(2,2-dimetilpropil)-L-α-glutamina

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Etapa A: *terc*-butil N^1-(2,2-dimetilpropil)-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 495.2; MS (ESI) *m/z* 989.4; HRMS: calculado para $C_{29}H_{38}N_2O_5$ + H+, 495.28535; encontrado (ESI-FTMS, $[M+H]^{1+}$), 495.2859.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(2,2-dimetilpropil)-L-α-glutaminato

MS (ESI) *m/z* 453.2; MS (ESI) *m/z* 905.4; HRMS: calculado para $C_{27}H_{36}N_2O_4$ + H+, 453.27478; encontrado (ESI-FTMS, $[M+H]^{1+}$), 453.2764.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(2,2-dimetilpropil)-L-α-glutamina

MS (ESI) *m/z* 397.1; MS (ESI) *m/z* 793.3; HRMS: calculado para $C_{23}H_{28}N_2O_4$ + H+, 397.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 397.21242.

Ejemplo 8VVV: N^2-(bifenil-4-ilcarbonil)-N^1-hexil-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-hexil-L-α-glutaminato

MS (ESI) *m/z* 509.3; MS (ESI) *m/z* 1017.5; HRMS: calculado para $C_{30}H_{40}N_2O_5$ + H+, 509.30100; encontrado (ESI-FTMS, $[M+H]^{1+}$), 509.30265.

Etapa B: *terc*-butil N^1-hexil-L-α-glutaminato

HRMS: calculado para $C_{15}H_{30}N_2O_3$ + H+, 287.23292; encontrado (ESI-FTMS, $[M+H]^{1+}$), 287.23282.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-hexil-L-α-glutaminato

MS (ESI) *m/z* 467.2; MS (ESI) *m/z* 933.4; HRMS: calculado para $C_{28}H_{38}N_2O_4$ + H+, 467.29043; encontrado (ESI-FTMS, $[M+H]^{1+}$), 467.29169.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-hexil-L-α-glutamina

MS (ESI) *m/z* 411.1; MS (ESI) *m/z* 821.3; HRMS: calculado para $C_{24}H_{30}N_2O_4$ + H+, 411.22783; encontrado (ESI-FTMS, $[M+H]^{1+}$), 411.22833.

Ejemplo 8WWW: N^2-(bifenil-4-ilcarbonil)-N^1-(5-hidroxipentil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(5- hidroxipentil)-L-α-glutaminato

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MS (ESI) *m/z* 511.2; MS (ESI) *m/z* 1021.4; HRMS: calculado para $C_{29}H_{38}N_2O_6$ + H+, 511.28026; encontrado (ESI-FTMS, $[M+H]^{1+}$), 511.28078.

Etapa B: *terc*-butil N^1-(5-hidroxipentil)-L-α-glutaminato

HRMS: calculado para $C_{14}H_{28}N_2O_4$ + H+, 289.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 289.21245.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(5-hidroxipentil)-L-α-glutaminato

HRMS: calculado para $C_{27}H_{36}N_2O_5$ + H+, 469.26970; encontrado (ESI-FTMS, $[M+H]^{1+}$), 469.27133.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(5-hidroxipentil)-L-α-glutamina

HRMS: calculado para $C_{23}H_{28}N_2O_5$ + H+, 413.20710; encontrado (ESI-FTMS, $[M+H]^{1+}$), 413.20657.

Ejemplo 8XXX: N^2-(bifenil-4-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(6- hidroxihexil)-L-α-glutaminato

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MS (ESI) *m/z* 525.2; MS (ESI) *m/z* 1049.4; HRMS: calculado para $C_{30}H_{40}N_2O_6$ + Na+, 547.27786; encontrado (ESI-FTMS, $[M+Na]^{1+}$), 547.27869.

Etapa B: *terc*-butil N^1-(6-hidroxihexil)-L-α-glutaminato

HRMS: calculado para $C_{15}H_{30}N_2O_4$ + H+, 303.22783; encontrado (ESI-FTMS, $[M+H]^{1+}$), 303.22841.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutaminato

HRMS: calculado para $C_{28}H_{38}N_2O_5$ + H+, 483.28535; encontrado (ESI-FTMS, $[M+H]^{1+}$), 483.28725.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutamina

HRMS: calculado para $C_{24}H_{30}N_2O_5$ + H+, 427.22275; encontrado (ESI-FTMS, $[M+H]^{1+}$), 427.22304.

Ejemplo 8YYY: N^2-(bifenil-4-ilcarbonil)-N^1-propil-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-propil-L-α-glutaminato

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MS (ESI) *m/z* 467.1; MS (ESI) *m/z* 933.1; MS (ESI) *m/z* 955.1; HRMS: calculado para $C_{27}H_{34}N_2O_5$ + H+, 467.25405; encontrado (ESI-FTMS, $[M+H]^{1+}$), 467.25527.

Etapa B: *terc*-butil N^1-propil-L-α-glutaminato

MS (ESI) *m/z* 245.1; MS (ESI) *m/z* 489.2; HRMS: calculado para $C_{12}H_{24}N_2O_3$ + H+, 245.18597; encontrado (ESI-FTMS, $[M+H]^{1+}$), 245.1861.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-propil-L-α-glutaminato

HRMS: calculado para $C_{25}H_{32}N_2O_4$ + H+, 425.24348; encontrado (ESI-FTMS, $[M+H]^{1+}$), 425.24455.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-propil-L-α-glutamina

HRMS: calculado para $C_{21}H_{24}N_2O_4$ + H+, 369.18088; encontrado (ESI-FTMS, $[M+H]^{1+}$), 369.18091.

Ejemplo 8ZZZ; N^2-(bifenil-4-ilcarbonil)-N^1-[4-(dimetilamino)bencil]-L-α-glutamina

Etapa A: *terc*-butil N^1-[4-(dimetilamino)bencil]-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 558.2; HRMS: calculado para $C_{33}H_{39}N_3O_5$ + H+, 558.29625; encontrado (ESI- FTMS, $[M+H]^{1+}$), 558.29668.

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Etapa B: *terc*-butil N^1-[4-(dimetilamino)bencil]-L-α-glutaminato

MS (ESI) *m/z* 336.2; MS (ESI) *m/z* 671.3; HRMS: calculado para $C_{18}H_{29}N_3O_3$ + H+, 336.22817; encontrado (ESI-FTMS, $[M+H]^{1+}$), 336.22836.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[4-(dimetilamino)bencil]-L-α-glutaminato

MS (ESI) *m/z* 516.2; HRMS: calculado para $C_{31}H_{37}N_3O_4$ + H+, 516.28568; encontrado (ESI- FTMS, $[M+H]^{1+}$), 516.28631.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-[4-(dimetilamino)bencil]-L-α-glutamina

MS (ESI) *m/z* 460.1; HRMS: calculado para $C_{27}H_{29}N_3O_4$ + H+, 460.22308; encontrado (ESI- FTMS, $[M+H]^{1+}$), 460.22347.

Ejemplo 8AAAA: N^1-(4-aminobencil)-N^2-(1,1'-bifenil-4-ilcarbonil)-1-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(4- nitrobencil)-L-α-glutaminato

MS (EST) *m/z* 560.3; MS (ESI) *m/z* 1119.5; HRMS: calculado para $C_{31}H_{33}N_3O_7$ + H+, 560.23913; encontrado (ESI_FTMS, $[M+H]^{1+}$), 560.23944.

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Etapa B: *terc*-butil N^1-(4-nitrobencil)-L-α-glutaminato

MS (ESI) *m/z* 338.2; HRMS: calculado para $C_{16}H_{23}N_3O_5$ + H+, 338.17105; encontrado (ESI- FTMS, $[M+H]^{1+}$), 338.17116.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-nitrobencil)-L-α-glutaminato

MS (ESI) *m/z* 518.2; MS (ESI) *m/z* 1035.5; HRMS: calculado para $C_{29}H_{31}N_3O_6$ + H+, 518.22856; encontrado (ESI-FTMS, $[M+H]^{1+}$), 518.22861.

Etapa C': Alquilación reductora de *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-nitrobencil)-L-α-glutaminato con 30% de formalina en agua y 10% de Pd/C da *terc*-butil N^1-(4-aminobencil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutaminato

MS (ESI) *m/z* 488.2; MS (ESI) *m/z* 975.4; HRMS: calculado para $C_{29}H_{33}N_3O_4$ + H+, 488.25438; encontrado (ESI_FTMS, $[M+H]^{1+}$), 488.2542.

Etapa D: N^1-(4-aminobencil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 432.2; HRMS: calculado para $C_{25}H_{25}N_3O_4$ + H+, 432.19178; encontrado (ESI_ FTMS, $[M+H]^{1+}$), 432.1915.

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Ejemplo 8BBBB: N^2-(bifenil-4-ilcarbonil)-N^1-[3-(dimetilamino)bencil]-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(3-nitrobencil)-L-α-glutaminato

MS (ESI) *m/z* 560.3; MS (ESI) *m/z* 1119.4; HRMS: calculado para $C_{31}H_{33}N_3O_7$ + H+, 560.23913; encontrado (ESI_FTMS, $[M+H]^{1+}$), 560.23892.

Etapa B: *terc*-butil N^1-(3-nitrobencil)-L-α-glutaminato

MS (ESI) *m/z* 338.1; MS (ESI) *m/z* 675.3; HRMS: calculado para $C_{16}H_{23}N_3O_5$ + H+, 338.17105; encontrado (ESI-FTMS, $[M+H]^{1+}$), 338.17102.

Etapa C: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-nitrobencil)-L-α-glutaminato

MS (ESI) *m/z* 518.2; MS (ESI) *m/z* 1035.4; HRMS: calculado para $C_{29}H_{31}N_3O_6$ + H+, 518.22856; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 518.22868.

Etapa C': Alquilación reductora de *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-nitrobencil)-L-α-glutaminato 30% de formalina y 10% Pd/C da *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[3-(dimetilamino)bencil]-L-α-glutaminato MS (ESI) *m/z* 516.2; HRMS: calculado para $C_{31}H_{37}N_3O_4$ + H+, 516.28568; encontrado (ESI-FTMS, $[M+H]^{1+}$), 516.28548.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-[3-(dimetilamino)bencil]-L-α-glutamina

MS (ESI) *m/z* 460.3; HRMS: calculado para $C_{27}H_{29}N_3O_4$ + H+, 460.22308; encontrado (ESI-FTMS, $[M+H]^{1+}$), 460.22304.

Ejemplo 8CCCC: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-nitrobencil)-L-α-glutamina

MS (ESI) *m/z* 462.2; MS (ESI) *m/z* 923.2; HRMS: calculado para $C_{25}H_{23}N_3O_6$ +H+, 462.16596; encontrado (ESI_FTMS, $[M+H]^{1+}$), 462.16599.

Ejemplo 8DDDD: N^1-(3-aminobencil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

HRMS: calculado para $C_{25}H_{25}N_3O_4$ + H+, 432.19178; encontrado (ESI_ FTMS, $[M+H]^{1+}$), 432.1917.

Ejemplo 8EEEE: N^1-bencil-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

Etapa A: *terc*-butil N^1-bencil-N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 458 (M-tBut).

Etapa B: *terc*-butil N^1-bencil-L-α-glutaminato

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MS (ESI) *m/z* 293.

Etapa C: *terc*-butil N^1-bencil-N^2-(1,1'-bifenil-4-ilcarbonil****L-α-glutaminato

MS (ESI) *m/z* 473.

Etapa D: N^1-bencil-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* All.

Ejemplo 8FFFF: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-D-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-D-α-glutaminato

Como se describió anteriormente de acuerdo con el procedimiento del Ejemplo 7, excepto que Fmoc-D-Glu-(OtBu)-OH se utiliza como material de partida para la primera etapa. HRMS: calculado para $C_{34}H_{39}FN_2O_5$ + H+, 575.29158; encontrado (ESI-FTMS, $[M+H]^{1+}$), 575.2927.

Etapa B: *terc*-butil N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-D-α-glutaminato

HRMS: calculado para $C_{19}H_{29}FN_2O_3$ + H+, 353.22350; encontrado (ESI-FTMS, $[M+H]^{1+}$), 353.22483.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-D-α-glutaminato

HRMS: calculado para $C_{32}H_{37}FN_2O_4$ + H+, 533.28101; encontrado (ESI-FTMS, $[M+H]^{1+}$), 533.28347.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-D-α-glutamina

MS (ESI) *m/z* 477.1; MS (ESI) *m/z* 499; MS (ESI) *m/z* 953.1; HRMS: calculado para $C_{28}H_{29}FN_2O_4$ + H+, 477.21841; encontrado (ESI-FTMS, $[M+H]^{1+}$), 477.21815.

Ejemplo 8GGGG: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-α-glutaminato

Como se describió anteriormente de acuerdo con el procedimiento del Ejemplo 7, excepto que Fmoc-DL-Glu-(OtBu)-OH (mezcla racémica) se utiliza como material de partida para la primera etapa. HRMS: calculado para $C_{34}H_{39}FN_2O_5$ + H+, 575.29158; encontrado (ESI-FTMS, $[M+H]^{1+}$), 575.29217.

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Etapa B: *terc*-butil N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-α-glutaminato

HRMS: calculado para $C_{19}H_{29}FN_2O_3$ + H+, 353.22350; encontrado (ESI-FTMS, $[M+H]^{1+}$), 353.22429.

Etapa C: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-α-glutaminato

HRMS: calculado para $C_{32}H_{37}FN_2O_4$ + H+, 533.28101; encontrado (ESI-FTMS, $[M+H]^{1+}$), 533.28268.

Etapa D: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-α-glutamina

MS (ESI) *m/z* 477.1; MS (ESI) *m/z* 953.1; HRMS: calculado para $C_{28}H_{29}FN_2O_4$ + H+, 477.21841; encontrado (ESI-FTMS, $[M+H]^{1+}$), 477.21805.

Ejemplo 8HHHH: ácido 4-Bencilcarbamoil-4-[4-(pirimidin-2-ilamino)-benzoilamino- butírico ácido terc-butírico

Etapa C: *terc*-butil éster de ácido 4-Bencilcarbamoil-4-[4-(pirimidin-2-ilamino)-benzoilamino-butírico

MS (ESI) *m/z* 488.

Etapa D: ácido 4-Bencilcarbamoil-4-[4-(pirimidin-2-ilamino)-benzoilamino-butírico ácido terc-butírico

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MS (ESI) *m/z* 432.

Ejemplo 8IIII: N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutamina

Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-{3-fenilpropil)-L-α-glutaminato

Se disuelve monohidrato de *terc*-butil éster de ácido 1,9(Fmoc)L-glutámico (1.33 g, 3.00 mmol) en DMF (8 mL) bajo nitrógeno. Se agrega BOP (1.33 g, 3.00 mmol) como un sólido, seguido por 3-fenil-1-propilamina (427 mL, 3 mmol). Finalmente se agrega en forma de gota DIEA (627 mL, 3.6 mmol). La reacción se monitorea por TLC, y se agita durante 24 hrs. La mezcla de reacción luego se agrega para agitar H_2O agitada (400 mL). Después de agitar durante 1 hora, se forman grupos de sólidos blancos. Los grupos se rompen con una espátula y se agita durante 30 minutos adicionales. El sólido se filtra y se lava con H_2O. El sólido luego se disuelve en CH_2Cl_2 y se seca con Na_2SO4. La solución se filtra y se concentra, dejando un sólido blanco. El sólido se disuelve en un mínimo de acetona y se agregan hexanos. Los disolventes luego se remueven y el sólido blanco se seca bajo vacío. Rendimiento 1.58 g de *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(3-fenilpropil)-L-α-glutaminato en 97% de rendimiento.

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MS (ESI) *m/z* 543.3; HRMS: calculado para $C_{33}H_{38}N_2O_5$ + H+, 543.2853; encontrado (ESI-FTMS, $[M+H]^{1+}$), 543.2847.

Etapa B: *terc*-butil N^1-(3-fenilpropil)-L-α-glutaminato

Se disuelve parcialmente *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(3-fenilpropil)-L-α-glutaminato (1.5 g, 2.76 mmol) en CH_3CN (15 mL). Se agrega DEA (2.9 mL, 27.6 mmol), que se disuelve completamente en 10 minutos. La reacción se monitorea por TLC y se completa en 2 hrs. El disolvente se remueve y el material restante se seca bajo vacío. El material se purifica en una columna de sílice corta utilizando 5% de Acetona/CH_2Cl_2 para eluir el subproducto Fmoc y luego 50% de Acetona/CH_2Cl_2 para eluir el producto. El aceite claro presente en el extremo se seca brevemente bajo vacío, y luego se toma en la siguiente etapa inmediatamente. Este nunca estuvo completamente libre de disolvente para la producción de *terc*- butil N^1-(3-fenilpropil)-L-α-glutaminato es 1.65 g, y se asume que es cuantitativo. MS (ESI) *m/z* 321.2; MS (ESI) *m/z* 641.4; HRMS: calculado para $C_{18}H_{28}N_2O_3$ + H+, 321.2173; encontrado (ESI-FTMS, $[M+H]^{1+}$), 321.2167.

Etapa C: *terc*-butil N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutaminato

Se disuelve *terc*-butil N^1-(3-fenilpropil)-L-α-glutaminato (350 mg, 1.09 mmol) en DMF (5 mL), en un frasco de 20 mL bajo nitrógeno. Se agregan ácido 2-fluorenocarboxílico (229 mg, 1.09 mmol) y BOP (530 mg, 1.20 mmol) como sólidos y

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disueltos. Finalmente se agrega DIEA (228 mL, 1.31 mmol), y la reacción se agita durante la noche. Se monitorea por TLC, la reacción se completa después de agitar durante la noche. La mezcla de reacción se agrega a H_2O (100 mL), se precipita un sólido amarillo pálido. El sólido se filtra y se seca en un secador durante la noche. Una vez seco, el sólido se toma en una pequeña cantidad de acetona, y se agregan hexanos para precipitar un sólido amarillo pálido. El sólido se filtra, se lava con hexanos y se seca en un secador. Rendimiento 293 mg de *terc*-butil N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutaminato a 52% de rendimiento. MS (ESI) *m/z* 513.3; MS (ESI) *m/z* 1025.6; MS (EST) *m/z* 535.3; HRMS: calculado para $C_{32}H_{36}N_2O_4$ + H+, 513.27478; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 513.2766.

Etapa D: N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutamina

Se disuelve *terc*-butil N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutaminato (273 mg, 0.533 mmol) en CH_2Cl_2 (1.5 mL). Se diluye TFA (1.23 mL, 16.0 mmol) en CH_2Cl_2 (2 mL) y luego se agrega lentamente a la primer solución. La reacción se monitorea por TLC y se completa en 2 hrs. El disolvente se remueve con un soplador de nitrógeno y el aceite amarillo restante se seca bajo vacío. El aceite amarillo luego se disuelve en un mínimo de acetona y se agrega hexanos precipitando un sólido blanco. El sólido se filtra, se lava con hexanos y luego se seca bajo vacío. La reacción produce 194 mg de N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(3-

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fenilpropil)-L-α-glutamina en 80% de rendimiento. MS (ESI) *m/z* 457.3; MS (ESI) *m/z* 913.5.

Ejemplo 8JJJJ: N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutamina

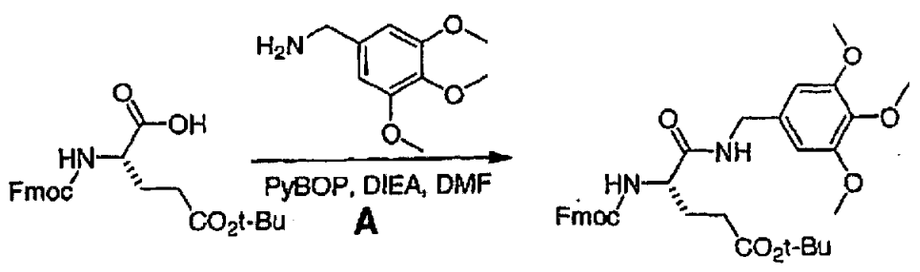
Etapa C: *terc*-butil N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutaminato

MS (ESI) *m/z* 513.3; MS (ESI) *m/z* 1025.6; HRMS: calculado para $C_{32}H_{36}N_2O_4$ + H+, 513.27478; encontrado (ESI-FTMS, $[M+H]^{1+}$), 513.27653.

Etapa D: N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutamina

MS (ESI) *m/z* 457.3; MS (ESI) *m/z* 913.5; MS (ESI) *m/z* 479.3.

Ejemplo 8KKKK: N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina



Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-(3,4,5-trimetoxibencil)-L-α-glutaminato

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MS (ESI) *m/z* 605.2; MS (ESI) *m/z* 1209.4; HRMS: calculado para $C_{34}H_{40}N_2O_8$ + H+, 605.28574; encontrado (ESI_FT, $[M+H]^{1+}$), 605.28453.

Etapa B: *terc*-butil N^1-(3,4,5-trimetoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 383.1; MS (ESI) *m/z* 765.3; HRMS: calculado para $C_{19}H_{30}N_2O_6$ + H+, 383.21766; encontrado (ESI_FT, $[MH-H]^{1+}$), 383.21755.

Etapa C: *terc*-butil N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 575.4; MS (ESI) *m/z* 1149.7; HRMS: calculado para $C_{33}H_{38}N_2O_7$ + H+, 575.27518; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 575.27604.

Etapa D: N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 519.3; MS (ESI) *m/z* 1037.6; HRMS: calculado para $C_{29}H_{30}N_2O_7$ + H+, 519.21258; encontrado (ESI-FTMS, $[M+H]^{1+}$), 519.2133.

Ejemplo 8LLLL: N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

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Etapa C: *terc*-butil N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 575.4; MS (ESI) *m/z* 1149.7; HRMS: calculado para $C_{33}H_{38}N_2O_7$ + H+, 575.27518; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 575.2761.

Etapa D: N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 519.3; MS (ESI) *m/z* 1037.6; MS (ESI) *m/z* 541.3; HRMS: calculado para $C_{29}H_{30}N_2O_7$ + H+, 519.21258; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 519.21329.

Ejemplo 8MMMM: N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

Etapa C: *terc*-butil N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-N^1-(3,4,5-trimetoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 589.4; MS (ESI) *m/z* 1177.7; MS (ESI) *m/z* 606.4; HRMS: calculado para $C_{33}H_{36}N_2O_8$ + H+, 589.25444; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 589.25507.

Etapa D: N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

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MS (ESI) *m/z* 531.3; MS (ESI) *m/z* 1063.5; HRMS: calculado para $C_{29}H_{28}N_2O_8$ + H+, 533.19184; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 533.19236.

Ejemplo 8NNNN; N^2-(4-fenoxibenzoil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

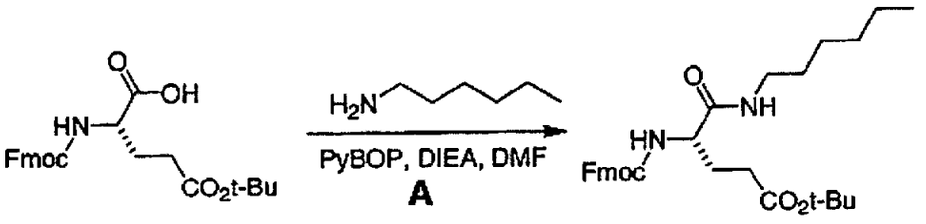
Etapa C: *terc*-butil N^2-(4-fenoxibenzoil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 579.3; MS (ESI) *m/z* 1157.7; HRMS: calculado para $C_{32}H_{38}N_2O_8$ + H+, 579.27009; encontrado (ESI-FTMS, $[M+H]^{1+}$), 579.2719.

Etapa D: N^2-(4-fenoxibenzoil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 523.3; MS (ESI) *m/z* 1045.5.

Ejemplo 80000: N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-hexil-L-α-glutamina



Etapa A: *terc*-butil N^2-[(9*H*-fluoren-9-ilmetoxi)carbonil]-N^1-hexil-L-α-glutaminato

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MS (ESI) *m/z* 509.3; MS (ESI) *m/z* 1017.5; HRMS: calculado para $C_{30}H_{40}N_2O_5$ + H+, 509.30100; encontrado (ESI-FTMS, $[M+H]^{1+}$), 509.30265.

Etapa B: *terc*-butil N^1-hexil-L-α-glutaminato

HRMS: calculado para $C_{15}H_{30}N_2O_3$ + H+, 287.23292; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 287.23282.

Etapa C: *terc*-butil N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-hexil-L-α-glutaminato

MS (ESI) *m/z* 479.1; MS (ESI) *m/z* 979.2; MS (ESI) *m/z* 501.1; HRMS: calculado para $C_{29}H_{38}N_2O_4$ + H+, 479.29043; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 479.29145.

Etapa D: N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-hexil-L-α-glutamina

MS (ESI) *m/z* 423.3; MS (ESI) *m/z* 845.6; MS (ESI) *m/z* 445.3.

Ejemplo 8PPPP: N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-hexil-L-α-glutamina

Etapa C: *terc*-butil N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-hexil-L-α-glutaminato

MS (ESI) *m/z* 479.1; MS (ESI) *m/z* 957.3; MS (ESI) *m/z* 979.2; HRMS: calculado para $C_{29}H_{38}N_2O_4$ + H+, 479.29043; encontrado (ESI-FTMS, $[M+H]^{1+}$), 479.29145.

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Etapa D: N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-hexil-L-α-glutamina

MS (ESI) *m/z* 423.3; MS (ESI) *m/z* 845.5; MS (ESI) *m/z* 445.3.

Ejemplo 8QQQQ: N^1-hexil-N^2-(4-fenoxibenzoil)-L-α-glutamina

Etapa C: *terc*-butil N^1-hexil-N^2-(4-fenoxibenzoil)-L-α-glutaminato

MS (ESI) *m/z* 483.1; MS (ESI) *m/z* 965.3; MS (ESI) *m/z* 987.3; HRMS: calculado para $C_{28}H_{38}N_2O_5$ + H+, 483.28535; encontrado (ESI-FTMS, $[M+H]^{1+}$), 483.28715.

Etapa D: N^1-hexil-N^2-(4-fenoxibenzoil)-L-α-glutamina

MS (ESI) *m/z* 427.3; MS (ESI) *m/z* 853.5; MS (ESI) *m/z* 449.3.

Ejemplo 8RRRR: N^1-hexil-N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-L-α-glutamina

Etapa C: *terc*-butil N^1-hexil-N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 493.1; MS (ESI) *m/z* 985.3; HRMS: calculado para $C_{29}H_{36}N_2O_5$ + H+, 493.26970; encontrado (ESI-FTMS, $[M+H]^{1+}$), 493.27119.

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Etapa D: N^1-hexil-N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 437.3; MS (ESI) *m/z* 873.5; MS (ESI) *m/z* 1309.8.

Ejemplo 8SSSS: N^2-(4-benzoilbenzoil)-N^1-bencil-L-α-glutamina

Etapa C: *terc*-butil N^2-(4-benzoilbenzoil)-N^1-bencil-L-α-glutaminato

MS (ESI) *m/z* 501.2; MS (ESI) *m/z* 523.2; HRMS: calculado para $C_{30}H_{32}N_2O_5$ + H+, 501.23840; encontrado (ESI+, $[M+H]^{1+}$), 501.23859.

Etapa D: N^2-(4-benzoilbenzoil)-N^1-bencil-L-α-glutamina

MS (ESI) *m/z* 445.2; HRMS: calculado para $C_{26}H_{24}N_2O_5$ + H+, 445.17580; encontrado (ESI+, $[MH-H]^{1+}$), 445.17619.

Ejemplo 8TTTT: N^1-(6-hidroxihexil)-N^2-(4-fenoxibenzoil)-L-α-glutamina

MS (ESI) *m/z* 443.2; MS (ESI) *m/z* 885.5; HRMS: calculado para $C_{24}H_3ON_2O_6$ + H+, 443.21766; encontrado (ESI-FTMS, $[M+H]^{1+}$), 443.21905.

Ejemplo 8UUUU: N^2-(9*H*-fluoren-9-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutamina

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MS (ESI) *m/z* 437.3; MS (ESI) *m/z* 551.3; HRMS: calculado para $C_{25}H_3ON_2O_5$ + H+, 439.22275; encontrado (ESI-FTMS, $[M+H]^{1+}$), 439.22374.

Ejemplo 8VVVV: N^2-(9*H*-fluoren-9-ilcarbonil)-N^1-(3,4,5-trimetoxibencil]-L-α-glutamina

MS (ESI) *m/z* 519.1; MS (ESI) *m/z* 1037.2; MS (ESI) *m/z* 536.1; HRMS: calculado para $C_{29}H_{30}N_2O_7$ + H+, 519.21258; encontrado (ESI-FTMS, $[M+H]^{1+}$), 519.213.

Ejemplo 8WWWW: N^2-(3-fenoxibenzoil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 523.1; MS (ESI) *m/z* 1045.2; MS (ESI) *m/z* 545.1; HRMS: calculado para $C_{28}H_{30}N_2O_8$ + H+, 523.20749; encontrado (ESI-FTMS, $[M+H]^{1+}$), 523.20712.

Ejemplo 8XXXX: N^2-(9*H*-fluoren-4-ilcarbonil)-N^1-(3,4,5-trimetoxibencil]-L-α-glutamina

MS (ESI) *m/z* 519.1; MS (ESI) *m/z* 1037.2; HRMS: calculado para $C_{29}H_{30}N_2O_7$ + H+, 519.21258; encontrado (ESI-FTMS, $[M+H]^{1+}$), 519.21308.

Ejemplo 8YYYY: N^1-adamantil-N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-L-α-glutamina

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MS (ESI) *m/z* 485.3; MS (ESI) *m/z* 971.6; MS (ESI) *m/z* 521.3; HRMS: calculado para $C_{29}H_{30}N_2O_5$ + H+, 487.22275; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 487.22272.

Ejemplo 8ZZZZ: N^1-1-adamantil-N^2-(4-fenoxibenzoil)-L-α-glutamina

MS (ESI) *m/z* 477.1; MS (ESI) *m/z* 953.3; MS (ESI) *m/z* 499.1; HRMS: calculado para $C_{28}H_{32}N_2O_5$ + H+, 477.23840; encontrado (ESI-FTMS, $[M+H]^{1+}$), 477.23857.

Ejemplo 8AAAAA: N^1-1-adamantil-N^2-(9*H*-fluoren-2-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 473.3; MS (ESI) *m/z* 945.5; HRMS: calculado para $C_{29}H_{32}N_2O_4$ +H+, 473.24348; encontrado (ESI-FTMS, $[M+H]^{1+}$), 473.24374.

Ejemplo 8BBBBB: N^1-1-adamantil-N^2-(9*H*-fluoren-9-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 471.3; MS (ESI) *m/z* 585.3; MS (ESI) *m/z* 943.6; HRMS: calculado para $C_{29}H_{32}N_2O_4$ + H+, 473.24348; encontrado (ESI-FTMS, $[M+H]^{1+}$), 473.2437.

Ejemplo 8CCCCC: N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(3-metilbencil)-L-α-glutamina

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HRMS: calculado para $C_{27}H_{26}N_2O_4$ + H+, 443.19653; encontrado (ESI- FTMS, $[M+H]^{1+}$), 443.1974.

Ejemplo 8DDDDD: N^1-(3-metilbencil)-N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-L-α-glutamina

HRMS: calculado para $C_{27}H_{24}N_2O_5$ + H+, 457.17580; encontrado (ESI- FTMS, $[MH-H]^{1+}$), 457.17616.

Ejemplo 8EEEEE: N^2-(9*H*-fluoren-9-ilcarbonil)-N^1-(3-metilbencil)-L-α-glutamina

HRMS: calculado para $C_{27}H_{26}N_2O_4$ + H+, 443.19653; encontrado (ESI- FTMS, $[M+H]^{1+}$), 443.19709.

Ejemplo 8FFFFF: N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-propil-L-α-glutamina

HRMS: calculado para $C_{22}H_{24}N_2O_4$ + H+, 381.18088; encontrado (ESI- FTMS, $[M+H]^{1+}$), 381.18117.

Ejemplo 8GGGGG: ácido 4-[(9H-fluoren-9-carbonil)-amino]-4-propilcarbamoil-butírico

MS (ESI) *m/z* 395.1; MS (ESI) *m/z* 789.2; MS (ESI) *m/z* 811.2; HRMS: calculado para $C_{22}H_{24}N_2O_4$ + H+, 381.18088; encontrado (ESI-FTMS, $[M+H]^{1+}$), 395.16097.

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Ejemplo 8HHHHH: ácido 4-[(9-Oxo-9H-fluoreno-2-carbonil)-amino1-4-propilcarbamoil-butírico

MS (ESI) *m/z* 381.1; MS (ESI) *m/z* 403.1; MS (ESI) *m/z* 761.2; HRMS: calculado para $C_{22}H_{22}N_2O_5$ + H+, 395.16015; encontrado (ESI-FTMS, $[M+H]^{1+}$), 381.18165.

Ejemplo 8IIIII; N^1-bencil-N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 441.2; MS (ESI) *m/z* 883.3; HRMS: calculado para $C_{26}H_{22}N_2O_5$ +H+, 443.16015; encontrado (ESI-FTMS, $[M+H]^{1+}$), 443.16063.

Ejemplo 8JJJJJ: N^1-bencil-N^2-(9*H*-fluoren-2-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 427.2; MS (ESI) *m/z* 855.3; HRMS: calculado para $C_{26}H_{24}N_2O_4$ + H+, 429.18088; encontrado (ESI-FTMS, $[M+H]^{1+}$), 429.18148.

Ejemplo 8KKKKK; N^1-bencil-N^2-(9*H*-fluoren-9-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 429; MS (ESI) *m/z* 857; MS (ESI) *m/z* 451; HRMS: calculado para $C_{26}H_{24}N_2O_4$ + H+, 429.18088; encontrado (ESI-FTMS, $[M+H]^{1+}$), 429.1815.

Ejemplo 8LLLLL: N^1-bencil-N^2-(3-fenoxibenzoil)-L-α-glutamina

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MS (ESI) *m/z* 433; MS (ESI) *m/z* 455; MS (ESI) *m/z* 865; HRMS: calculado para $C_{25}H_{24}N_2O_5$ + H+, 433.17580; encontrado (ESI-FTMS, $[M+H]^{1+}$), 433.17696.

Ejemplo 8MMMMM: *N*^{1}-(1-metil-1-feniletil)-*N*^{2}-[(9-oxo-9*H*-fluoren-2-ilcarbonil]-L-α-glutamina

MS (ESI) *m/z* 471.2; MS (ESI) *m/z* 941.5; MS (ESI) *m/z* 493.2; HRMS: calculado para $C_{28}H_{26}N_2O_5$ + H+, 471.19145; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 471.19271.

Ejemplo 8NNNNN: *N*^{2}-(9*H*-fluoren-9-ilcarbonil)-*N*^{1}-(1-metil-1-feniletil)-L-α-glutamina

MS (ESI) *m/z* 455.1; MS (ESI) *m/z* 911.3; HRMS: calculado para $C_{28}H_{28}N_2O_4$ + H+, 457.21218; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 457.214.

Ejemplo 8OOOOO: *N*^{1}-(1-metil-1-feniletil)-N^2(3-fenoxibenzoil)-L-α-glutamina

MS (ESI) *m/z* 461.2; MS (ESI) *m/z* 921.5; MS (ESI) *m/z* 483.2; HRMS: calculado para $C_{27}H_{28}N_2O_5$ + H+, 461.20710; encontrado (ESI-FTMS, $[M+H]^{1+}$), 461.20882.

Ejemplo 8PPPPP: N^2-(bifenil-4-ilcarbonil)-N1-[1S)-1-feniletil]-L-α-glutamina

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MS (ESI) *m/z* 431.2; MS (ESI) *m/z* 861.4; MS (ESI) *m/z* 453.2; HRMS: calculado para $C_{26}H_{26}N_2O_4$ + H+, 431.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 431.19802.

Ejemplo 8QQQQQ; *N*^{2}-(9*H*-fluoren-2-ilcarbonil)-*N*^{1}-[(1S)-1-feniletil]-L-α-glutamina

MS (ESI) *m/z* 443.2; MS (ESI) *m/z* 885.4; MS (ESI) *m/z* 465.2; HRMS: calculado para $C_{27}H_{26}N_2O_4$ + H+, 443.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 443.19772.

Ejemplo 8RRRRR; *N*^{2}-(bifenil-4-ilcarbonil)-N1-[(1S)-1-(4-fluorofenil)etil]-L-α-glutamina

MS (ESI) *m/z* 449.2; MS (ESI) *m/z* 897.4; HRMS: calculado para $C_{26}H_{25}FN_2O_4$ + H+, 449.18711; encontrado (ESI-FTMS, $[M+H]^{1+}$), 449.18839.

Ejemplo 8SSSSS: *terc*-butil *N*^{2}-(bifenil-4-ilcarbonil)-N^1-(1-feniletil)-L-α-glutaminato

MS(ESI) *m/z* 505.3.

Ejemplo 8TTTTT: *N*^{2}-(bifenil-4-ilcarbonil)-*N*^{1}-[(1R)-1-(4-fluorofenil)etil]-L-α-glutamina

MS (ESI) *m/z* 449.2; MS (ESI) *m/z* 897.5; MS (ESI) *m/z* 471.2; HRMS: calculado para $C_{26}H_{25}FN_2O_4$ + H+, 449.18711; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 449.18679.

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Ejemplo 8UUUUU: N^2-(bifenil-4-ilcarbonil)-N^1-[(1R)-1-feniletil]-L-α-glutamina

MS (ESI) *m/z* 431.2; MS (ESI) *m/z* 861.5; MS (ESI) *m/z* 453.2; HRMS: calculado para $C_{26}H_{26}N_2O_4$ + H+, 431.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 431.19828.

Ejemplo 8VVVVV: N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-[(1R)-1-feniletil]-L-α-glutamina

MS (ESI) *m/z* 443.2; MS (ESI) *m/z* 885.5; MS (ESI) *m/z* 465.2; HRMS: calculado para $C_{27}H_{26}N_2O_4$ + H+, 443.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 443.19676.

Ejemplo 8WWWWW: N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(hidroxihexil)-L-α-glutamina

MS (ESI) *m/z* 437.3; MS (ESI) *m/z* 875.5; HRMS: calculado para $C_{25}H_{30}N_2O_5$ +H+, 439.22275; encontrado (ESI-FTMS, $[M+H]^{1+}$), 439.22313.

Ejemplo 8XXXXX: N^1-(6-hidroxihexil)-N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 453.2; HRMS: calculado para $C_{25}H_{28}N_2O_6$ + H+, 453.20201; encontrado (ESI-FTMS, $[M+H]^{1+}$), 453.2027.

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Ejemplo 8YYYYY: N^2-(bifenil-4-ilcarbonil)-N^1-9*H*-fluoren-9-il-L-α-glutamina

MS (ESI) *m/z* 489.1; MS (ESI) *m/z* 979.2; HRMS: calculado para $C_{31}H_{26}N_2O_4$ +H+, 491.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 491.19778.

Ejemplo 8ZZZZZ: N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 489.2; MS (ESI) *m/z* 977.4; HRMS: calculado para $C_{29}H_{29}FN_2O_4$ + H+, 489.21841; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 489.21827.

Ejemplo 8AAAAAA: *N*-(1-adamantilmetil)-N^2-(bifenil-4-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 475.2; MS (ESI) *m/z* 949.5; HRMS: calculado para $C_{29}H_{34}N_2O_4$ +H+, 475.25913; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 475.25916.

Ejemplo 8BBBBBB: N-[(1S)-1-bencil-2-hidroxietill-N^2-(9H-fluoren-2-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 473.2; MS (ESI) *m/z* 945.4; HRMS: calculado para $C_{28}H_{28}N_2O_5$ +H+, 473.20710; encontrado (ESI-FTMS, $[M+H]^{1+}$), 473.2073.

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Ejemplo 8CCCCCC: N^2-(bifenil-4-ilcarbonil)-*N*-metil-*N*-(2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 445.4; MS (ESI) *m/z* 889.7; HRMS: calculado para $C_{27}H_{28}N_2O_4$ +H+, 445.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 445.21312.

Ejemplo 8DDDDDD: N^2-(9*H*-fluoren-2-ilcarbonil)-*N*-metil-*N*-(2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 457.4; MS (ESI) *m/z* 913.7; HRMS: calculado para $C_{28}H_{28}N_2O_4$ + H+, 457.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 457.21146.

Ejemplo 8EEEEEE; N^2-(bifenil-4-ilcarbonil)-*N*-butil-*N*-metil-L-α-glutamina

MS (ESI) *m/z* 397.2; MS (ESI) *m/z* 793.4; MS (ESI) *m/z* 419.2; HRMS: calculado para $C_{23}H_{28}N_2O_4$ + H+, 397.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 397.21249.

Ejemplo 8FFFFFF: *N*-butil-N^2-(9*H*-fluoren-2-ilcarbonil)-*N*-metil-L-α-glutamina

MS (ESI) *m/z* 409.3; MS (ESI) *m/z* 817.5; HRMS: calculado para $C_{24}H_{28}N_2O_4$ +H+, 409.21218; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 409.21227.

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Ejemplo 8GGGGGG; N^2-(bifenil-4-ilcarbonil)-*N*-[2-(3,4-dimetoxifenil)etil1-*N*-metil-L-α-glutamina

MS (ESI) *m/z* 505.3; MS (ESI) *m/z* 527.3; MS (ESI) *m/z* 1009.6; HRMS: calculado para $C_{29}H_{32}N_2O_6$ + H+, 505.23331; encontrado (ESI-FTMS, $[M+H]^{1+}$), 505.23512.

Ejemplo 8HHHHHH: N^2-[4-(1,3-benzodioxol-5-il)benzoil]-N-[2-(4-fluorofenil)-1,1-dimetiletili-L-α-glutamina

MS (ESI) *m/z* 521.1; MS (ESI) *m/z* 1041.3; HRMS: calculado para $C_{29}H_{29}FN_2O_6$ + H+, 521.20824; encontrado (ESI-FTMS, $[M+H]^{1+}$), 521.20872.

Ejemplo IIIIII: N[2-(3,4-dimetoxifenil)etil]-N^2-(9H-fluoren-2-ilcarbonil)-N-metil-1-α-glutamina

MS (ESI) *m/z* 517.2; MS (ESI) *m/z* 1033.3; HRMS: calculado para $C_{30}H_{32}N_2O_6$ + H+, 517.23331; encontrado (ESI-FTMS, $[M+H]^{1+}$), 517.23342.

Ejemplo 8JJJJJJ: N^2-(9*H*-fluoren-2-ilcarbonil)-N-[(2R)-2-fenilpropill-L-α-glutamina

MS (ESI) *m/z* 457.2; MS (ESI) *m/z* 913.3; MS (ESI) *m/z* 479.1; HRMS: calculado para $C_{28}H_{28}N_2O_4H$- H+, 457.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 457.21246.

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Ejemplo 8KKKKKK: N^2-(bifenil-4-ilcarbonil)-N-[(2R)-2-fenilpropil]-L-α-glutamina

MS (ESI) *m/z* 445.2; MS (ESI) *m/z* 889.3; HRMS: calculado para $C_{27}H_{28}N_2O_4$ +H+, 445.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 445.21285.

Ejemplo 8LLLLLL: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-L-glutamamida

MS (ESI) *m/z* 476.2; MS (ESI) *m/z* 951.5; HRMS: calculado para $C_{28}H_{30}FN_3O_3$ +H+, 476.23440; encontrado (ESI-FTMS, $[M+H]^{1+}$), 476.23543.

Ejemplo 8MMMMMM: N-[(1S)-1-bencil-2-hidroxietil]-N^2-(bifenil-4-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 461.2; MS (ESI) *m/z* 921.4; MS (ESI) *m/z* 943.4; HRMS: calculado para $C_{27}H_{28}N_2O_5$ + H+, 461.20710; encontrado (ESI-FTMS, $[M+H]^{1+}$), 461.20748.

Ejemplo 8NNNNNN: N^1-bencil-N^2-(4-bromobenzoil)-L-α-glutamina

MS (ESI) *m/z* 419.1; MS (ESI) *m/z* 837.2; HRMS: calculado para $C_{19}H_{19}BrN_2O_4$ + H+, 419.06009; encontrado (ESI_FT, $[M+H]^{1+}$), 419.05998.

Ejemplo 8000000: N^1-[2-(acetilamino)etil]-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 410.2; MS (ESI) *m/z* 821.5; HRMS: calculado para $C_{22}H_{25}N_3O5$ +H+, 412.18670; encontrado (ESI_FT, $[M+H]^{1+}$), 412.18628.

Ejemplo 8PPPPPP; N^2-(1,1'-bifenil-4-ilacetil)-N^1-(3-metoxibencil]-L-α-glutamina

El compuesto del título se prepara de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 7, excepto que ácido bifenilacético se utiliza. MS (ESI) *m/z* 461.2; MS (ESI) *m/z* 921.4; HRMS: calculado para $C_{27}H_{28}N_2O_5$ + H+, 461.20710; encontrado (ESI_ FTMS, $[M+H]^{1+}$), 461.20514.

Ejemplo 8QQQQQQ: N^1-(2-bencilfenil)-N^2-(1,1'-bifenil-4-ilcarbonil]-L-α-glutamina

MS (ESI-) *m/z* 491.3; HRMS: calculado para $C_{31}H_{28}N_2O_4$ + H+, 493.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 493.21319.

Ejemplo 8RRRRRR: N^2-2-naftoil-N^1-(3-fenilpropil)-L-α-glutamina

MS (ESI) *m/z* 419.1; MS (ESI) *m/z* 837.1; MS (ESI) *m/z* 441.1; HRMS: calculado para $C_{25}H_{26}N_2O_4$ + H+, 419.19653; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 419.19678.

Ejemplo 8SSSSSS: *N*^{2}-[(9-oxo-9*H*-fluoren-2-il)carbonil]-*N*^{1}-(3-fenilpropil)-L-α-glutamina

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MS (ESI) *m/z* 471.3; MS (ESI) *m/z* 941.5; HRMS: calculado para $C_{28}H_{26}N_2O_5$ +H+, 471.19145; encontrado (ESI-FTMS, $[M+H]^{1+}$), 471.19142.

Ejemplo 8TTTTTT: N^2-(4-fenoxibenzoil)-N^1-(3-fenilpropil)-L-α-glutamina

HRMS: calculado para $C_{27}H_{28}N_2O_5$ + H+, 461.20710; encontrado (ESI- FTMS, $[M+H]^{1+}$), 461.20673.

Ejemplo 8UUUUUU: N1-bencil-N2-[4-(pirimidin-2-ilamino)benzoil]-L-α-glutamina

MS *m/z* 02-101699GMS.

Ejemplo 8VVVVVV: N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutamina

MS (ES]) *m/z* 439.2; HRMS: calculado para $C_{25}H_{30}N_2O_5$ + H+, 439.22275; encontrado (ESI-FTMS, $[M+H]^{1+}$), 439.22379.

Ejemplo 8WWWWWW: N^2-[4-(5-bromo-2-tienil)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 561.3; MS (ESI) *m/z* 1121.5; HRMS: calculado para $C_{26}H_{26}BrFN_2O_4S$ + H+, 561.08534; encontrado (ESI-FTMS, $[M+H]^{1+}$), 561.08472.

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Ejemplo 8XXXXXX: *N*-[2-(5-cloro-2-tienil)-1,1-dimetiletil]-N^2-[(3'-fluorobifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1033.5; MS (ESI) *m/z* 539.3; HRMS: calculado para $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; encontrado (ESI-FTMS, $[M+H]^{1+}$), 517.13517.

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1033.6; MS (ESI) *m/z* 539.3; HRMS: calculado para $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; encontrado (ESI-FTMS, $[M+H]^{1+}$), 517.13686.

Ejemplo 8YYYYYY: N^2-[(3',4'-difluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 513.4; MS (ESI) *m/z* 1025.7; MS (ESI) *m/z* 535.3; HRMS: calculado para $C_{28}H_{27}F_3N_2O_4$ + H+, 513.19957; encontrado (ESI-FTMS, $[M+H]^{1+}$), 513.19837.

MS (ESI) *m/z* 513.4; MS (ESI) *m/z* 1025.8; MS (ESI) *m/z* 535.4; HRMS: calculado para $C_{28}H_{27}F_3N_2O_4$ + H+, 513.19957; encontrado (ESI-FTMS, $[M+H]^{1+}$), 513.20152.

Ejemplo 8ZZZZZZ: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(3',4'-difluorobifenil-4-yI)carbonil]-L-α-glutamina

MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.5; HRMS: calculado para $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; encontrado (ESI-FTMS, $[M+H]^{1+}$), 529.16931.

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Ejemplo 8AAAAAAA: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(2',4'-difluorobifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.5; HRMS: calculado para $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; encontrado (ESI-FTMS, $[M+H]^{1+}$), 529.16951.

Ejemplo 8BBBBBBB: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(2',5'-difluorobifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 529.3; MS (ESI) *m/z* 1057.5; MS (ESI) *m/z* 551.2; HRMS: calculado para $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; encontrado (ESI-FTMS, $[M+H]^{1+}$), 529.16954.

Ejemplo 8CCCCCCC: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(2',6'-difluorobifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.4; HRMS: calculado para $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; encontrado (ESI-FTMS, $[M+H]^{1+}$), 529.16943.

Ejemplo 8DDDDDDD: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(3',5'-difluorobifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 529.3; MS (ESI) *m/z* 1057.5; MS (ESI) *m/z* 551.3; HRMS: calculado para $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; encontrado (ESI-FTMS, $[M+H]^{1+}$), 529.17191.

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Ejemplo 8EEEEEEE: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(2',3'-difluorobifenil-4-il)carbonil]-L-α-glutamina

HRMS: calculado para $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; encontrado (ESI- FTMS, $[MH-H]^{1+}$), 529.17167.

Ejemplo 8FFFFFFF; *N*-(1,1-dimetil-2-feniletil)-N^2-(4-pirimidin-5-ilbenzoil)-L-α-glutamina

MS (ESI) *m/z* 461.2; MS (ESI) *m/z* 921.4; HRMS: calculado para $C_{26}H_{28}N_4O_4$ +H+, 461.21833; encontrado (ESI-FTMS, $[M+H]^{1+}$), 461.21863.

Ejemplo 8GGGGGGG: N^2-[(3',4'-difluorobifenil-4-il)carbonil]-*N*-1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 495.2; MS (ESI) *m/z* 989.4; HRMS: calculado para $C_{28}H_{28}F_2N_2O_4$ +H+, 495.20899; encontrado (ESI-FTMS, $[M+H]^{1+}$), 495.21035.

Ejemplo 8HHHHHHH: N^2-[(3',5'-difluorobifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 495.2; MS (ESI) *m/z* 989.4; MS (ESI) *m/z* 517.2; HRMS: calculado para $C_{28}H_{28}F_2N_2O_4$ + H+, 495.20899; encontrado (ESI-FTMS, $[M+H]^{1+}$), 495.21017.

Ejemplo 8IIIIIII: *N*-[2-(5-cloro-2-tienil-1,1-dimetiletil]-N^2-[(3',4'-difluorobifenil-4-il)carbonil]-L-α-glutamina

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MS (ESI) *m/z* 533.3; MS (ESI) *m/z* 1067.7; HRMS: calculado para $C_{26}H_{25}ClF_2N_2O_4S$ + H+, 535.12644; encontrado (ESI-FTMS, $[M+H]^{1+}$), 535.1267.

Ejemplo 8JJJJJJJ: N^2-(bifenil-4-ilcarbonil)-*N*-[2-(5-cloro-2-tienil]-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 499.4; MS (ESI) *m/z* 997.7; MS (ESI) *m/z* 521.4; HRMS: calculado para $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; encontrado (ESI-FTMS, $[M+H]^{1+}$), 499.14616.

Ejemplo 8KKKKKKK: N^2-{[5-(3-cloro-4-fluorofenil)-2-tienil]carbonil}-*N*-[2-(5-cloro-2-tienil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 557.3; MS (ESI) *m/z* 1113.6; HRMS: calculado para $C_{24}H_{23}Cl_2FN_2O_4S_2$ + H+, 557.05331; encontrado (ESI-FTMS, $[M+H]^{1+}$), 557.05439.

Ejemplo 8LLLLLLL; N^2-{[4'-(hidroximetil)bifenil-4-il]carbonil}-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 537.1; MS (ESI) *m/z* 1073.3; HRMS: calculado para $C_{29}H_{32}N_2O_8$ +H+, 537.22314; encontrado (ESI-FTMS, $[M+H]^{1+}$), 537.22326.

Ejemplo 8MMMMMMM: N^2-{[4'-(bromometil)bifenil-4-il]carbonil}-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

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MS (ESI) *m/z* 599.1; MS (ESI) *m/z* 1197.1; HRMS: calculado para $C_{29}H_{31}BrN_2O_7$ + H+, 599.13874; encontrado (ESI-FTMS, $[M+H]^{1+}$), 599.13934.

Ejemplo 8NNNNNNN: *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[4-(2-tienil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 483.3; MS (ESI) *m/z* 965.5; HRMS: calculado para $C_{26}H_{27}FN_2O_4S$ + H+, 483.17483; encontrado (ESI-FTMS, $[M+H]^{1+}$), 483.1743.

Ejemplo 80000000: *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[4-(2-furil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 467.3; MS (ESI) *m/z* 933.6; HRMS: calculado para $C_{26}H_{27}FN_2O_5$ + H+, 467.19768; encontrado (ESI-FTMS, $[M+H]^{1+}$), 467.19704.

Ejemplo 8PPPPPPP: N^2-{[4'-(hidroximetil)bifenil-4-ilcarbonil}-*N*-(3-metilbencil)-L-α-glutamina

MS (ESI) *m/z* 459.1; MS (ESI) *m/z* 919.5; HRMS: calculado para $C_{27}H_{28}N_2O_5$ +H+, 461.20710; encontrado (ESI-FTMS, $[M+H]^{1+}$), 461.20822.

Ejemplo 80000000: N^2-{[3'-(hidroximetil)bifenil-4-il]carbonil}-*N*-(3-metilbencil)-L-α-glutamina

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MS (ESI) *m/z* 459.2; HRMS: calculado para $C_{27}H_{28}N_2O_5$ + H+, 461.20710; encontrado (ESI-FTMS, $[M+H]^{1+}$), 461.20807.

Ejemplo 8RRRRRRR: *N*^{2}-[4-(2,3-dihidro-1-benzofurano-5-il)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1035.7; HRMS: calculado para $C_{30}H_{31}FN_2O_5$ +H+, 519.22898; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 519.22989.

Ejemplo 8SSSSSSS: *N*^{2}-[(3'-cloro-4'-fluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 529.3; MS (ESI) *m/z* 1057.6; HRMS: calculado para $C_{28}H_{27}ClF_2N_2O_4$ + H+, 529.17002; encontrado (ESI-FTMS, $[M+H]^{1+}$), 529.17061.

Ejemplo 8TTTTTTT: *N*^{2}-{[3'-(bromometil)bifenil-4-il]carbonil}-*N*-(3-metilbencil)-L-α-glutamina

MS (ESI) *m/z* 521.1; HRMS: calculado para $C_{27}H_{27}BrN_2O_4$ + H+, 523.12270; encontrado (ESI-FTMS, $[M+H]^{1+}$), 523.12235.

Ejemplo 8UUUUUUU; *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-*N*^{2}-[4-(3-tienil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 483.1; MS (ESI) *m/z* 965.3; HRMS: calculado para $C_{26}H_{27}FN_2O_4S$ + H+, 483.17483; encontrado (ESI-FTMS, $[M+H]^{1+}$), 483.17572.

Ejemplo 8VVVVVVV: *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[4-(5-metil-2-tienil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 495.4; MS (ESI) *m/z* 991.7; HRMS: calculado para $C_{27}H_{29}FN_2O_4S$ + H+, 497.19048; encontrado (ESI-FTMS, $[M+H]^{1+}$), 497.19118.

Ejemplo 8WWWWWWW: N^2-[4-(5-cloro-2-tienil)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 515.3; MS (ESI) *m/z* 1031.7; HRMS: calculado para $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; encontrado (ESI-FTMS, $[M+H]^{1+}$), 517.13644. MS (ESI) *m/z* 515.3; MS (ESI) *m/z* 1031.6; HRMS: calculado para $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; encontrado (ESI-FTMS, $[M+H]^{1+}$), 517.13658.

Ejemplo 8XXXXXXX: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(2-tienil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 497.3; MS (ESI) *m/z* 995.6; HRMS: calculado para $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; encontrado (ESI-FTMS, $[M+H]^{1+}$), 499.14509.

Ejemplo 8YYYYYYY: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-{[5-(3-metoxifenil)-2-tienil]carbonil}-L-α-glutamina

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MS (ESI) *m/z* 529.3; MS (ESI) *m/z* 1057.5; HRMS: calculado para $C_{27}H_{29}ClN_2O_5S$ + H+, 529.15585; encontrado (ESI-FTMS, $[M+H]^{1+}$), 529.15608.

Ejemplo 8ZZZZZZZ: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(5-fenil-2-tienil)carbonil]-L-α-glutamina

MS (ESI) *m/z* 499.2; MS (ESI) *m/z* 997.5; HRMS: calculado para $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; encontrado (ESI-FTMS, $[M+H]^{1+}$), 499.14644.

Ejemplo 8AAAAAAAA: N^2-(2,2'-bitien-5-ilcarbonil)-*N*-[2-(4-clorofenil)-1,1-dimetiletili-L-α-glutamina

MS (ESI) *m/z* 505.1; MS (ESI) *m/z* 1009.1; HRMS: calculado para $C_{24}H_{25}ClN_2O_4S_2$ + H+, 505.10170; encontrado (ESI-FTMS, $[M+H]^{1+}$), 505.10282.

Ejemplo 8BBBBBBBB: N^2-[4-(2,3-dihidro-1-benzofurano-6-il)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 517.5; MS (ESI) *m/z* 1035.9; HRMS: calculado para $C_{30}H_{31}FN_2O_5$ +H+, 519.22898; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 519.22971.

Ejemplo 8CCCCCCCC: *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-{[6-(3-metoxifenil)piridin-3-il]carbonil}-L-α-glutamina

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MS (ESI) *m/z* 508.4; HRMS: calculado para $C_{28}H_{30}FN_3O_5$ + H+, 508.22423; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 508.22472.

Ejemplo 8DDDDDDDD; *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 478.4; HRMS: calculado para $C_{27}H_{28}FN_3O_4$ + H+, 478.21366; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 478.21435.

Ejemplo 8EEEEEEEE: *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(5-fenil-2-tienil)carbonil]-L-α-glutamina

MS (ESI) *m/z* 483.2; MS (ESI) *m/z* 965.4; HRMS: calculado para $C_{26}H_{27}FN_2O_4S$ + H+, 483.17483; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 483.17576.

Ejemplo 8FFFFFFFF: N^2-[(3-fluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 495.3; MS (ESI) *m/z* 989.6; HRMS: calculado para $C_{28}H_{28}F_2N_2O_4$ +H+, 495.20899; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 495.20963.

Ejemplo 8GGGGGGGG: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(5-piridin-4-il-2-tienil)carbonil]-L-α-glutamina

MS (ESI) *m/z* 500.3; HRMS: calculado para $C_{25}H_{26}ClN_3O_4S$ + H+, 500.14053; encontrado (ESI-FTMS, $[M+H]^{1+}$), 500.13984.

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Ejemplo 8HHHHHHHH: N^2-{[5-(3-cloro-4-fluorofenil)-2-tienil]carbonil}-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 549.3; HRMS: calculado para $C_{26}H_{25}Cl_2FN_2O_4S$ + H+, 551.09689; encontrado (ESI-FTMS, $[M+H]^{1+}$), 551.09834.

Ejemplo 8IIIIIIII: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(2,3-dihidro-1-benzofurano-6-il)benzoil]-L-α-glutamina

MS (ESI) *m/z* 535.4; MS (ESI) *m/z* 1069.8; HRMS: calculado para $C_{30}H_{31}ClN_2O_5$ + H+, 535.19943; encontrado (ESI-FTMS, $[M+H]^{1+}$), 535.20047.

Ejemplo 8JJJJJJJJJ: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(5-piridin-3-il-2-tienil)carbonil}-L-α-glutamina

MS (ESI) *m/z* 500.3; HRMS: calculado para $C_{25}H_{26}ClN_3O_4S$ + H+, 500.14053; encontrado (ESI-FTMS, $[M+H]^{1+}$), 500.1423.

Ejemplo 8KKKKKKKK: N^2-[4-(2,3-dihidro-1-benzofurano-6-il)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 501.4; MS (ESI) *m/z* 1001.8; HRMS: calculado para $C_{30}H_{32}N_2O_5$ + H+, 501.23840; encontrado (ESI-FTMS, $[M+H]^{1+}$), 501.23954.

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Ejemplo 8LLLLLLL: N^2-{[5-(3-cloro-4-fluorofenil)-2-tienil]carbonil}-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 515.3; MS (ESI) *m/z* 1031.7; HRMS: calculado para $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; encontrado (ESI-FTMS, $[M+H]^{1+}$), 517.13443.

Ejemplo 8MMMMMMMM: *N*-(1,1-dimetil-2-feniletil)-N^2-[4-(2-tienil)benzoil1-L-α-glutamina

MS (ESI) *m/z* 465.2; MS (ESI) *m/z* 929 A; HRMS: calculado para $C_{26}H_{28}N_2O_4S$ +H+, 465.18425; encontrado (ESI-FTMS, $[M+H]^{1+}$), 465.18402.

Ejemplo 8NNNNNNNN: *N*-(1,1-dimetil-2-feniletil)-N^2-{[5-(3-metoxifenil)-2-tienil]carbonil}-L-α-glutamina

MS (ESI) *m/z* 495.2; MS (ESI) *m/z* 989.4; HRMS: calculado para $C_{27}H_{30}N_2O_5S$ + H+, 495.19482; encontrado (ESI-FTMS, $[M+H]^{1+}$), 495.1942.

Ejemplo 800000000: *N*-(1,1-dimetil-2-feniletil)-N^2-[(5-fenil-2-tienil)carbonil]-L-α-glutamina

MS (ESI) *m/z* 465.2; MS (ESI) *m/z* 929.4; HRMS: calculado para $C_{26}H_{28}N_2O_4S$ + H+, 465.18425; encontrado (ESI-FTMS, $[M+H]^{1+}$), 465.18359.

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Ejemplo 8PPPPPPPP: N^2-(2,2'-bitien-5-ilcarbonil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 469.3; MS (ESI) *m/z* 939.6; HRMS: calculado para $C_{24}H_{26}N_2O_4S_2$ + H+, 471.14067; encontrado (ESI-FTMS, $[M+H]^{1+}$), 471.1403.

Ejemplo 8QQQQQQQQ; *N*-(1,1-dimetil-2-feniletil)-N^2-[(5-piridin-4-il-2-tienil)carbonil]-L-α-glutamina

MS (ESI) *m/z* 466.4; HRMS: calculado para $C_{25}H_{27}N_3O_4S$ + H+, 466.17950; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 466.17836.

Ejemplo 8RRRRRRRR: *N*-(1,1-dimetil-2-feniletil)-N^2-[(5-piridin-3-il-2-tienil)carbonil]-L-α-glutamina

MS (ESI) *m/z* 466.3; HRMS: calculado para $C_{25}H_{27}N_3O_4S$ + H+, 466.17950; encontrado (ESI-FTMS, $[M+H]^{1+}$), 466.17912.

Ejemplo 8SSSSSSSS: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(5-cloro-2-tienil)benzoil]-L-α-glutamina

HRMS: calculado para $C_{26}H_{26}Cl_2N_2O_4S$ + H+, 533.10631; encontrado (ESI- FTMS, $[MH-H]^{1+}$), 533.10629.

Ejemplo 8TTTTTTTT: N^2-{[6-(5-cloro-2-tienil)piridin-3-il)carbonil}-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

525

MS (ESI) *m/z* 500.3; MS (ESI) *m/z* 999.6; HRMS: calculado para $C_{25}H_{26}ClN_3O_4S$ + H+, 500.14053; encontrado (ESI-FTMS, $[M+H]^{1+}$), 500.14123.

Ejemplo 8UUUUUUUU: *N*-(1,1-dimetil-2-feniletil)-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 460.4; HRMS: calculado para $C_{27}H_{29}N_3O_4$ + H+, 460.22308; encontrado (ESI-FTMS, $[M+H]^{1+}$), 460.22319.

Ejemplo 8VVVVVVVV: *N*-[2-(4-clorofenil)-1,1-dimetiletill-N^2-(5-fenil-2-furoil)-L-α-glutamina

MS (ESI) *m/z* 483.3; MS (ESI) *m/z* 965.6; MS (ESI) *m/z* 987.6; HRMS: calculado para $C_{26}H_{27}ClN_2O_5$ + H+, 483.16813; encontrado (ESI-FTMS, $[M+H]^{1+}$), 483.16818.

Ejemplo 8WWWWWWWW: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-{[6-(5-cloro-2-tienil)piridin-3-il]carbonil)-L-α-glutamina

MS (ESI) *m/z* 534.3; HRMS: calculado para $C_{25}H_{25}Cl_2N_3O_4S$ + H+, 534.10156; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 534.10123.

Ejemplo 8XXXXXXXX: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 494.4; HRMS: calculado para $C_{27}H_{28}ClN_3O_4$ + H+, 494.18411; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 494.18423.

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Ejemplo 8YYYYYYYY: *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-{[5-(3-metoxifenil)-2-tienil]carbonil}-L-α-glutamina

MS (ESI) *m/z* 513.3; MS (ESI) *m/z* 1025.7; HRMS: calculado para $C_{27}H_{29}FN_2O_5S$ + H+, 513.18540; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 513.18635.

Ejemplo 8ZZZZZZZZ: *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(5-piridin-3-il-2-tienil)carbonil]-L-α-glutamina

MS (ESI) *m/z* 484.3; HRMS: calculado para $C_{25}H_{26}FN_3O_4S$ + H+, 484.17008; encontrado (ESI-FTMS, $[M+H]^{1+}$), 484.17109.

Ejemplo 8AAAAAAAAA: N^2-{[5-(3-cloro-4-fluorofenil)-2-tienil]carbonil)-*N*-[2-(4-fluorofenil)-1,1-dimetiletill-L-α-glutamina

MS (ESI) *m/z* 535.2; MS (ESI) *m/z* 557.2; MS (ESI) *m/z* 1069.5; HRMS: calculado para $C_{26}H_{25}ClF_2N_2O_4S$ + H+, 535.12644; encontrado (ESI-FTMS, $[M+H]^{1+}$), 535.12696.

MS (ESI) *m/z* 533.3; MS (ESI) *m/z* 1067.6; HRMS: calculado para $C_{26}H_{25}ClF_2N_2O_4S$ + H+, 535.12644; encontrado (ESI-FTMS, $[M+H]^{1+}$), 535.12796.

Ejemplo 8BBBBBBBBB: N^2-(2,2'-bitien-5-ilcarbonil)-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

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MS (ESI) *m/z* 489.3; MS (ESI) *m/z* 977.5; HRMS: calculado para $C_{24}H_{25}FN_2O_4S_2$ + H+, 489.13125; encontrado (ESI-FTMS, $[M+H]^{1+}$), 489.13208.

Ejemplo 8CCCCCCCCC: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(5-formil-2-tienil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 527.1; MS (ESI) *m/z* 1053.1; MS (ESI) *m/z* 549; HRMS: calculado para $C_{27}H_{27}ClN_2O_5S$ + H+, 527.14020; encontrado (ESI-FTMS, $[M+H]^{1+}$), 527.14185.

Ejemplo 8DDDDDDDDD: N^2-[4-(5-acetil-2-tienil)benzoil]-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 541.1; MS (ESI) *m/z* 1081.2; MS (ESI) *m/z* 563.1; HRMS: calculado para $C_{28}H_{29}ClN_2O_5S$ + H+, 541.15585; encontrado (ESI-FTMS, $[M+H]^{1+}$), 541.15471.

Ejemplo 8EEEEEEEE: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(1,3-tiazol-2-il)benzoil]-L-α-glutamina

MS (ESI) *m/z* 500.3; HRMS: calculado para $C_{25}H_{26}ClN_3O_4S$ + H+, 500.14053; encontrado (ESI-FTMS, $[M+H]^{1+}$), 500.14163.

Ejemplo 8FFFFFFFF: *N*-(1,1-dimetil-2-feniletil)-N^2-[4-(1,3-tiazol-2-il)benzoil]-1-α-glutamina

MS (ESI) *m/z* 4663; HRMS: calculado para $C_{25}H_{27}N_3O_4S$ + H+, 466.17950; encontrado (ESI-FTMS, $[M+H]^{1+}$), 466.18052.

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Ejemplo 8GGGGGGGGG: *N*-(1,1-dimetil-2-feniletil)-N^2-(5-fenil-2-furoil)-L-α-glutamina

MS (ESI) *m/z* 449.3; MS (ESI) *m/z* 897.6; MS (ESI) *m/z* 471.3; HRMS: calculado para $C_{26}H_{28}N_2O_5$ + H+, 449.20710; encontrado (ESI-FTMS, $[M+H]^{1+}$), 449.20772.

Ejemplo 8HHHHHHHHH; *N*-(1,1-dimetil-2-feniletil)-N^2-[4-(5-formil-2-tienil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 493.3; MS (ESI) *m/z* 985.6; MS (ESI) *m/z* 515.3; HRMS: calculado para $C_{27}H_{28}N_2O_5S$ + H+, 493.17917; encontrado (ESI-FTMS, $[M+H]^{1+}$), 493.18011.

Ejemplo 8IIIIIIIII: N^2-[4-(5-acetil-2-tienil)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 507.3; MS (ESI) *m/z* 1013.7; MS (ESI) *m/z* 529.3; HRMS: calculado para $C_{28}H_{30}N_2O_5S$ + H+, 507.19482; encontrado (ESI-FTMS, $[M+H]^{1+}$), 507.19518.

Ejemplo 8JJJJJJJJJ: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[3-(5-cloro-2-tienil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 533.3; MS (ESI) *m/z* 1065.5; MS (ESI) *m/z* 555.3; HRMS: calculado para $C_{26}H_{26}Cl_2N_2O_4S$ + H+, 533.10631; encontrado (ESI-FTMS, $[M+H]^{1+}$), 533.10835.

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Ejemplo 8KKKKKKKKK: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[3-(2-tienil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 499.3; MS (ESI) *m/z* 997.6; MS (ESI) *m/z* 521.3; HRMS: calculado para $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; encontrado (ESI-FTMS, $[M+H]^{1+}$), 499.14679.

Ejemplo 8LLLLLLLLL: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-{[5-[4-clorofenil)-2-tienil]carbonil}-L-α-glutamina

MS (ESI) *m/z* 533.3; MS (ESI) *m/z* 1065.5; MS (ESI) *m/z* 555.3; HRMS: calculado para $C_{26}H_{26}Cl_2N_2O_4S$ + H+, 533.10631; encontrado (ESI-FTMS, $[M+H]^{1+}$), 533.10784.

Ejemplo 8MMMMMMMMM: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-{[5-(4-fluorofenil)-2-tienil)carbonil}-L-α-glutamina

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 539.3; MS (ESI) *m/z* 1033.6; HRMS: calculado para $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; encontrado (ESI-FTMS, $[M+H]^{1+}$), 517.13691.

Ejemplo 8NNNNNNNNN: N^2-[4-(5-bromo-2-tienil)benzoil]-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 577.2; MS (ESI) *m/z* 1153.4; HRMS: calculado para $C_{26}H_{26}BrClN_2O_4S$ + H+, 577.05579; encontrado (ESI-FTMS, $[M+H]^{1+}$), 577.05597.

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Ejemplo 8000000000: N^2-[4-(5-bromo-2-tienil)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 543.1; MS (ESI) *m/z* 1085.2; HRMS: calculado para $C_{26}H_{27}BrN_2O_4S$ + H+, 543.09477; encontrado (ESI-FTMS, $[M+H]^{1+}$), 543.0965; HRMS: calculado para $C_{26}H_{27}BrN_2O_4S$ + H+, 543.09477; encontrado (ESI-FTMS, $[M+H]^{1+}$), 543.09494.

Ejemplo 8PPPPPPPPP: *N*-(1,1-dimetil-2-feniletil)-N^2-{[5-(4-fluorofenil)-2-tienil]carbonil}-L-α-glutamina

MS (ESI) *m/z* 483.2; MS (ESI) *m/z* 965.4; MS (ESI) *m/z* 505.2; HRMS: calculado para $C_{26}H_{27}FN_2O_4S$ + H+, 483.17483; encontrado (ESI-FTMS, $[M+H]^{1+}$), 483.17634.

Ejemplo 8QQQQQQQQQ: N^2-[3-(5-cloro-2-tienil)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 499.2; MS (ESI) *m/z* 997.3; MS (ESI) *m/z* 521.1; HRMS: calculado para $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; encontrado (ESI-FTMS, $[M+H]^{1+}$), 499.14544.

Ejemplo 8RRRRRRRRR: *N*-(1,1-dimetil-2-feniletil)-N^2-[3-(2-tienil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 465.2; MS (ESI) *m/z* 929.4; MS (ESI) *m/z* 487.2; HRMS: calculado para $C_{26}H_{28}N_2O_4S$ + H+, 465.18425; encontrado (ESI-FTMS, $[M+H]^{1+}$), 465.18439.

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Ejemplo 8SSSSSSSSS: N^2-[(3'-clorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletill-L-α-glutamina

HRMS: calculado para $C_{28}H_{28}ClFN_2O_4$ + H+, 511.17944; encontrado (ESI- FTMS, $[M+H]^{1+}$), 511.17974.

Ejemplo 8TTTTTTTTT: N^2-[(4'-clorobifenil-4-il)carbonil]-N-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

HRMS: calculado para $C_{28}H_{28}ClFN_2O_4$ + H+, 511.17944; encontrado (ESI- FTMS, $[M+H]^{1+}$), 511.17972.

Ejemplo 8UUUUUUUUU: N^2-[(4'-fluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

HRMS: calculado para $C_{28}H_{28}F_2N_2O_4$ + H+, 495.20899; encontrado (ESI- FTMS, $[MH-H]^{1+}$), 495.20933.

Ejemplo 8VVVVVVVVV: N^2-[(3'-fluorobifenil-4-ilcarbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

HRMS: calculado para $C_{28}H_{28}F_2N_2O_4$ + H+, 495.20899; encontrado (ESI- FTMS, $[M+H]^{1+}$), 495.20937.

Ejemplo 8WWWWWWWWW: *N*-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(3-fenil-2-tienil)carbonil]-L-α-glutamina

HRMS: calculado para $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; encontrado (ESI- FTMS, $[MH-H]^{1+}$), 499.14664.

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Ejemplo 8XXXXXXXXX: N^2-[(4'-clorobifenil-4-il)carbonil]-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 527.3; MS (ESI) *m/z* 1053.7; MS (ESI) *m/z* 549.3; HRMS: calculado para $C_{28}H_{28}Cl_2N_2O_4$ + H+, 527.14989; encontrado (ESI-FTMS, $[M+H]^{1+}$), 527.15049.

HRMS: calculado para $C_{28}H_{28}Cl_2N_2O_4$ + H+, 527.14989; encontrado (ESI- FTMS, $[M+H]^{1+}$), 527.14931.

Ejemplo 8YYYYYYYYY: N^2-[(3'-clorobifenil-4-il)carbonil]-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 527.3; MS (ESI) *m/z* 1053.7; MS (ESI) *m/z* 549.3; HRMS: calculado para $C_{28}H_{28}Cl_2N_2O_4$ + H+, 527.14989; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 527.15048.

Ejemplo 8ZZZZZZZZZ: *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-{[5-(4-fluorofenil)-2-tienil]carbonil}-L-α-glutamina

MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.6; MS (ESI) *m/z* 523.3; HRMS: calculado para $C_{26}H_{26}F_2N_2O_4S$ + H+, 501.16541; encontrado (ESI-FTMS, $[M+H]^{1+}$), 501.16642.

MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.6; MS (ESI) *m/z* 523.3; HRMS: calculado para $C_{26}H_{26}F_2N_2O_4S$ + H+, 501.16541; encontrado (ESI-FTMS, $[M+H]^{1+}$), 501.16709.

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Ejemplo 8AAAAAAAAAA: N^2-{[5-(4-clorofenil)-2-tienil]carbonil}-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 499.1; MS (ESI) *m/z* 997.2; HRMS: calculado para $C_{26}H_{27}ClN_2O_4S$ + H+, 499.14528; encontrado (ESI-FTMS, $[M+H]^{1+}$), 499.14552.

Ejemplo 8BBBBBBBBBB: *N*-(1,1-dimetil-2-feniletil)-N^2-[(3-fenil-2-tienil)carbonil]-L-α-glutamina

MS (ESI) *m/z* 465.2; MS (ESI) *m/z* 929.4; MS (ESI) *m/z* 951.4; HRMS: calculado para $C_{26}H_{28}N_2O_4S$ + H+, 465.18425; encontrado (ESI-FTMS, $[M+H]^{1+}$), 465.18455.

Ejemplo 8CCCCCCCCCC: N^2-(4-bromobenzoil)-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 479.3; MS (ESI) *m/z* 957.5; MS (ESI) *m/z* 501.2; HRMS: calculado para $C_{22}H_{24}BrFN_2O_4$ + H+, 479.09762; encontrado (ESI-FTMS, $[M+H]^{1+}$), 479.0983.

Ejemplo 8DDDDDDDDDD: *N*-(1,1-dimetil-2-feniletil]-N^2-[(4'-fluorobifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 477.3; MS (ESI) *m/z* 499.3; MS (ESI) *m/z* 953.7; HRMS: calculado para $C_{28}H_{29}FN_2O_4$ + H+, 477.21841; encontrado (ESI-FTMS, $[M+H]^{1+}$), 477.21891.

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Ejemplo 8EEEEEEEEEE: *N*-(1,1-dimetil-2-feniletil)-N^2-[(3'-fluorobifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 477.3; MS (ESI) *m/z* 499.3; MS (ESI) *m/z* 953.7; HRMS: calculado para $C_{28}H_{29}FN_2O_4$ + H+, 477.21841; encontrado (ESI-FTMS, $[M+H]^{1+}$), 477.21875.

Ejemplo 8FFFFFFFFFF: N^2-[4-(5-cloro-2-tienil)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-D-α-glutamina

MS (ESI) *m/z* 517.2; MS (ESI) *m/z* 539.2; MS (ESI) *m/z* 1033.5; HRMS: calculado para $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; encontrado (ESI-FTMS, $[M+H]^{1+}$), 517.1365.

Ejemplo 8GGGGGGGGGG: N^2-[6-(5-cloro-2-tienil)piridin-3-il]carbonil}-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 518.2; HRMS: calculado para $C_{25}H_{25}ClFN_3O_4S$ + H+, 518.13111; encontrado (ESI-FTMS, $[M+H]^{1+}$), 518.13169.

Ejemplo 8HHHHHHHHHH: N^2-{[5-(4-clorofenil)-2-tienil]carbonil}-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 539.3; MS (ESI) *m/z* 1033.6; HRMS: calculado para $C_{26}H_{26}ClFN_2O_4S$ + H+, 517.13586; encontrado (ESI-FTMS, $[M+H]^{1+}$), 517.1363.

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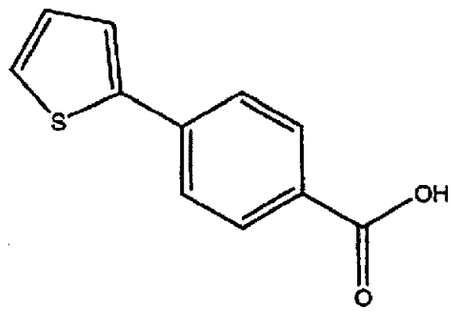
Ejemplo 8IIIIIIIIII: N^2-{[5-(3,4-difluorofenil)-2-tienil]carbonil}-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 519.3; MS (ESI) *m/z* 1037.7; MS (ESI) *m/z* 541.3; HRMS: calculado para $C_{26}H_{25}F_3N_2O_4S$ + H+, 519.15599; encontrado (ESI-FTMS, $[M+H]^{1+}$), 519.1568.

Los siguientes intermedios (R_1COOH en el esquema 7) se preparan y utilizan en la preparación de algunos de los compuestos del Ejemplo 8:

Ejemplo 8JJJJJJJJJJ: ácido 4-(2-tienil)benzoico



Se disuelven ácido 4-yodobenzoico (3 g, 12.1 mmol), ácido 2-tiofeneborónico (3.10 g, 24.2 mmol), y $Pd(PPh_3)_4$ (1.4 g, 1.21 mmol) en DMF (75 mL) en un recipiente de presión de tapa rosca de 350 mL . En un frasco separado, se disuelve K_2CO_3 (5.02 g, 36.3 mmol) en H_2O (12 mL) y luego se agrega a la reacción. El frasco se sella, se calienta a 100° C y se agita durante la noche (17h).

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La reacción luego se diluye con H_2O (150 mL), se coloca en un embudo de sep., y se agrega NaOH 1N para elevar el pH a 10. La capa acuosa se lava con EtOAc (2x250 mL). La capa acuosa se mantiene, se agrega carbón vegetal activado, y la mezcla se calienta y se agita. Se agrega Celita, seguido por la mezcla que se filtra a través de celita. El filtrado luego se acidifica con HCl concentrado. En pH 7 un sólido tostado empieza a precipitar. El pH se baja a 5 y el sólido formado se filtra. El sólido se disuelve parcialmente en una cantidad pequeña de tolueno, que luego se remueve para quitar algo del agua aún presente. Esta etapa se repite, luego el sólido se seca bajo vacío. Rendimiento - 2.01 g sólido tostado, 81%. MS (ESI) *m/z* 202.9; HRMS: calculado para $C_{11}H_8O_2S$ + H+, 205.03178; encontrado (ESI-FTMS, $[M+H]^{1+}$), 205.03127.

Los siguientes compuestos se preparan de acuerdo con el procedimiento similar al descrito en el Ejemplo 8JJJJJJJJJJ, a partir de reactivos disponibles comercialmente apropiados:

i: ácido 5-(3-metoxifenil)tiofen-2-carboxílico

MS (ESI) *m/z* 233.1; HRMS: calculado para $C_{12}H_{10}O_3S$ + H+, 235.04234; encontrado (ESI- FTMS, $[M+H]^{1+}$), 235.04226;

ii. ácido 2,2'-bitiofen-5-carboxílico

MS (ESI) *m/z* 209.1; HRMS: calculado para $C_9H_6O_2S_2$ + H+, 210.98820; encontrado (ESI- FTMS, $[M+H]^{1+}$), 210.98816;

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iii. ácido 5-piridin-4-iltiofen-2-carboxílico

MS (ESI) *m/z* 206.1; HRMS: calculado para $C_{10}H_7NO_2S$ + H+, 206.02703; encontrado (ESI- FTMS, $[M+H]^{1+}$), 206.02691;

iv. ácido 4-(5-cloro-2-tienil)benzoico

HRMS: calculado para $C_{11}H_7ClO_2S$ - H+, 236.97825; encontrado (ESI-FTMS, $[M-H]^{1-}$), 236.97751;

v. ácido 5-fenil-2-furóico

HRMS: calculado para $C_{11}H_8O_3$ + H+, 189.05462; encontrado (ESI-FTMS, $[M+H]^{1+}$), 189.05445;

vi. ácido 4-(5-acetil-2-tienil)benzoico

MS (ESI) *m/z* 245.1; HRMS: calculado para $C_{13}H_{10}O_3S$ + H+, 247.04234; encontrado (ESI- FTMS, $[MH-H]^{1+}$), 247.04223;

vii. ácido 3-(5-cloro-2-tienil)benzoico

MS (ESI) *m/z* 237; HRMS: calculado para $C_{11}H_7ClO_2S$ - H+, 236.97825; encontrado (ESI- FTMS, $[M-H]^{1-}$), 236.97757;

viii. ácido 3-(2-tienil)benzoico

MS (ESI) *m/z* 203.1; HRMS: calculado para $C_{11}H_8O_2S$ + H+, 205.03178; encontrado (ESI- FTMS, $[M+H]^{1+}$), 205.03194;

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ix. ácido 5-(4-clorofenil)tiofen-2-carboxílico

MS (ESI) *m/z* 237; MS (ESI) *m/z* 283; MS (ESI) *m/z* 475.1; HRMS: calculado para $C_{11}H_7ClO_2S$ - H+, 236.97825; encontrado (ESI-FTMS, $[M-H]^{1-}$), 236.97825;

x. ácido 3-feniltiofen-2-carboxílico

MS (ESI) *m/z* 203.1; MS (ESI) *m/z* 249.1; HRMS: calculado para $C_{11}H_8O_2S$ + H+, 205.03178; encontrado (ESI-FTMS, $[M+H]^{1+}$), 205.03177;

xi. ácido 4'-clorobifenil-4-carboxílico

MS (ESI) *m/z* 231.1; HRMS: calculado para $C_{13}H_9ClO_2$ - H+, 231.02183; encontrado (ESI- FTMS, $[M-H]^{1-}$), 231.02129;

xii. ácido 3'-clorobifenil-4-carboxílico

MS (ESI) *m/z* 231.1; HRMS: calculado para $C_{13}H_9ClO_2$ - H+, 231.02183; encontrado (ESI- FTMS, $[M-H]^{1-}$), 231.02128;

xiii. ácido 5-(3,4-difluorofenil)tiofen-2-carboxílico

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MS (ESI) *m/z* 239; MS (ESI) *m/z* 285.1; MS (ESI) *m/z* 479.1; HRMS: calculado para $C_{11}H_6F_2O_2S$ + H+, 241.01293; encontrado (ESI-FTMS, $[M+H]^{1+}$), 241.01183;

xiv. ácido 5-(2,4-difluorofenil)tiofen-2-carboxílico

MS (ESI) *m/z* 239; MS (ESI) *m/z* 285; HRMS: calculado para $C_{11}H_6F_2O_2S$ + H+, 241.01293; encontrado (ESI-FTMS, $[M+H]^{1+}$), 241.01187;

xv. ácido 4-fenoxibenzoico

MS (ESI) *m/z* 213.1; HRMS: calculado para $C_{13}H_{10}O_3$ + H+, 215.07027; encontrado (ESI- FTMS, $[M+H]^{1+}$), 215.07029;

xvi. ácido 4-(2,3-dihidro-1-benzofurano-6-il)benzoico

MS (ESI) *m/z* 239.1; HRMS: calculado para $C_{15}H_{12}O_3$ - H+, 239.07137; encontrado (ESI- FTMS, $[M-H]^{1-}$), 239.07131;

xvii. ácido 5-(3-cloro-4-fluorofenil)tiofen-2-carboxílico

MS (ESI) *m/z* 255.1; MS (ESI) *m/z* 511.2; HRMS: calculado para $C_{11}H_6ClFO_2S$ - H+, 254.96883; encontrado (ESI-FTMS, $[M-H]^{1-}$), 254.96892;

xviii. ácido 5-piridin-3-iltiofen-1-carboxílico

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MS (ESI) *m/z* 206.1; HRMS: calculado para $C_{10}H_7NO_2S$ + H+, 206.02703; encontrado (ESI- FTMS, $[M+H]^{1+}$), 206.02708;

xix. ácido 6-(5-cloro-2-tienil)nicotínico

MS (ESI) *m/z* 238;

XX. ácido 6-fenilnicotínico

MS (ESI) *m/z* 200.1; HRMS: calculado para $C_{12}H_9NO_2$ + H+, 200.07061; encontrado (ESI- FTMS, $[M+H]^{1+}$), 200.07052;

xxi. ácido 4-(1,3-tiazol-2-il)benzoico

pf 235 - 237° C; MS (ESI) *m/z* 206; MS (ESI) *m/z* 204;

xxii. ácido 4-(5-bromo-2-tienil)benzoico

MS (ESI) *m/z* 281; MS (ESI) *m/z* 394.8;

xxiii. ácido 5-(4-fluorofenil)tiofen-2-carboxílico

MS (ES) *m/z* 221.0; MS (ES) *m/z* 443.0;

xxiv. ácido 4-[5-(aminosulfonil)-2-tienil]benzoico

MS (ESI) *m/z* 282.1; MS (ESI) *m/z* 565.2;

xxv. ácido 4-(5-ciano-2-tienil)benzoico

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MS (ESI) *m/z* 228.1;

xxvi. ácido 3'-fluorobifenil-carboxílico

MS (ESI) *m/z* 215.1;

xxvii. ácido 3',4'-difluorobifenil-4-carboxílico

MS (EST) *m/z* 233;

xxviii. ácido 2',4'-difluorobifenil-4-carboxílico

MS (ESI) *m/z* 233.1;

xxix. ácido 2',5'-difluorobifenil-4-carboxílico

MS (ESI) *m/z* 233.1;

XXX. ácido 3',5'-difluorobifenil-4-carboxílico

MS (ESI) *m/z* 233.1;

xxxi. ácido 2',6'-difluorobifenil-4-carboxílico

MS (ESI) *m/z* 233.1;

xxxii. ácido 2',3'-difluorobifenil-4-carboxílico

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MS (ESI) *m/z* 233;

xxxiii. ácido 4-(5-metil-2-tienil)benzoico

MS (ESI) *m/z* 217.1; HRMS: calculado para $C_{12}H_{10}O_2S$ + H+, 219.04743; encontrado (ESI- FTMS, $[M+H]^{1+}$), 219.04744;

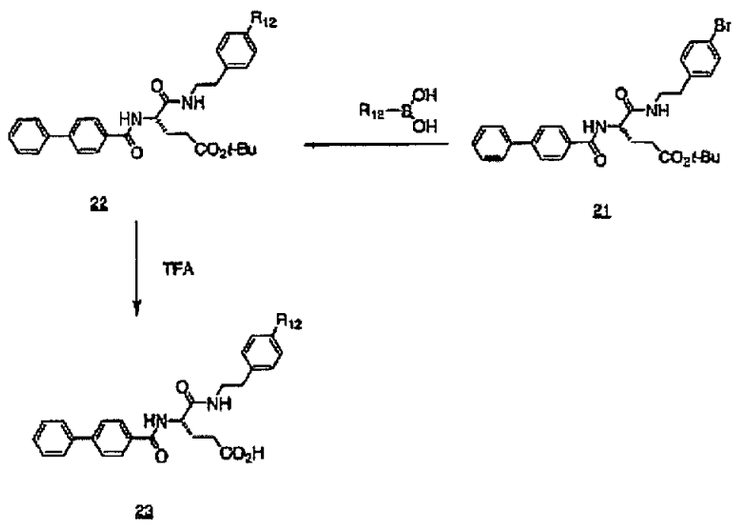
xxxiv. ácido 6-(3-metoxifenil)nicotínico

MS (ESI) *m/z* 230.1;

xxxv. ácido 3-fluorobifenil-4-carboxílico

MS (ESI) *m/z* 215.1; HRMS: calculado para $C_{13}H_9FO_2$ + H+, 217.06593; encontrado (ESI- FTMS, $[M+H]^{1+}$), 217.06598.

Esquema 8



Ejemplo 9: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-4-il)etil]-L-α-glutamina

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Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-4-il)etil]-L-α-glutaminato

Se disuelve *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-bromofenil)etil]-L-α-glutaminato (333 mg, 0.59 mmol, 1 equiv.) en DME (5 mL) y la mezcla se agrega a ácido 4-formilfenil borónico (0.97 g, 0.65 mmol, 1.1 equiv.) y $Pd(PPh_3)_4$ (68 mg, 0.059 mmol, 0.1 equiv.) y se agita durante 30 minutos antes de la adición de K_2CO_3 ac. (163 mg, 1.18 mmol, 2 equiv.) en 1 mL de H_2O. La mezcla se tapa en un recipiente sellado y se agita durante la noche a 80° C. La reacción se completa como se determina mediante TLC. La mezcla se filtra sobre celita, el disolvente se remueve, y el sólido tostado resultante se diluye con EtOAc (20 mL) y se lava consecutivamente con H_2O, 10% de HCl, solución salina, y se seca sobre Na_2SO_4. El sólido se purifica mediante cromatografía de columna (gel de sílice, 41% Acetona/Hexanos) para dar 38 mg de *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-4-il)etil]-L-α-glutaminato en 11% de rendimiento.

MS (ESI) *m/z* 591.3; MS (ESI) *m/z* 1181.5; HRMS: calculado para $C_{37}H_{38}N_2O_5$ + H+, 591.28535; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 591.28473.

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-4-il)etil]-L-α-glutamina

Se disuelve *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-4-il)etil]-L-α-glutaminato (100 mg, 0.17 mmol,

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1 equiv.) en CH_2Cl_2 (5 mL) y se agrega a TFA (2 mL). La mezcla se agita a temperatura ambiente durante 3 hrs. La reacción se completa como se determina mediante TLC. El disolvente se remueve y el sólido resultante se purifica mediante HPLC preparativo para dar N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-4-il)etil]-L-α-glutamina en 89% de rendimiento (80 mg). MS (ESI) *m/z* 533.1; HRMS: calculado para $C_{33}H_{30}N_2O_5$ + H+, 535.22275; encontrado (ESI-FTMS, $[M+H]^{1+}$), 535.22464.

Ejemplo 10:

Los siguientes compuestos se preparan de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 9.

Ejemplo 10A: N^2-(bifenil-4-ilcarbonil)-N^1-(2-[4'-(trifluorometil)bifenil-4-il]etil}-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4'-(trifluorometil)bifenil-4-il]etil}-L-α-glutaminato

MS (ESI) *m/z* 631.2; MS (ESI) *m/z* 1261.4; MS (ESI) *m/z* 653.2; HRMS: calculado para $C_{37}H_{37}F_3N_2O_4$ + H+, 631.27782; encontrado (ESI-FTMS, $[M+H]^{1+}$), 631.27719.

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4'-(trifluorometil)bifenil-4-il]etil}-L-α-glutamina

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HRMS: calculado para $C_{33}H_{29}F_3N_2O_4$ + H+, 575.21522; encontrado (ESI-FTMS, $[M+H]^{1+}$), 575.21548.

Ejemplo 10B: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-metoxibifenil-4-il)etil]-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-metoxibifenil-4-il)etil]-L-α-glutaminato

MS (ESI) *m/z* 593.3; MS (ESI) *m/z* 1185.5; HRMS: calculado para $C_{37}H_{40}N_2O_5$ + H+, 593.30100; encontrado (ESI-FTMS, $[M+H]^{1+}$), 593.29946.

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-metoxibifenil-4-il)etil]-L-α-glutamina

HRMS: calculado para $C_{33}H_{32}N_2O_5$ + H+, 537.23840; encontrado (ESI-FTMS, $[M+H]^{1+}$), 537.23906.

Ejemplo 10C: N^2-(bifenil-4-ilcarbonil)-N^1-(2-bifenil-4-iletil)-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(2-bifenil-4-iletil)-L-α-glutaminato

MS (ESI) *m/z* 563.3; MS (ESI) *m/z* 1125.5; HRMS: calculado para $C_{36}H_{38}N_2O_4$ + H+, 563.29043; encontrado (ESI-FTMS, $[M+H]^{1+}$), 563.28977.

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Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-(2-bifenil-4-iletil)-L-α-glutamina

HRMS: calculado para $C_{32}H_{30}N_2O_4$ + H+, 507.22783; encontrado (ESI-FTMS, $[M+H]^{1+}$), 507.22688.

Ejemplo 10D: N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4-(2-tienil)fenil]etil}-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4-(2-tienil)fenil]etil}-L-α-glutaminato

MS (ESI) *m/z* 569.2; MS (ESI) *m/z* 1137.4; HRMS: calculado para $C_{34}H_{36}N_2O_4S$ + H+, 569.24685; encontrado (ESI-FTMS, $[M+H]^{1+}$), 569.24702.

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4-(2-tienil)fenil]etil}-L-α-glutamina

MS (ESI) *m/z* 511.1; HRMS: calculado para $C_{30}H_{28}N_2O_4S$ + H+, 513.18425; encontrado (ESI-FTMS, $[M+H]^{1+}$), 513.18417.

Ejemplo 10E: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2'-etoxibifenil-4-il)etil]-L-α-glutamina

MS (ESI) *m/z* 551.1; MS (ESI) *m/z* 1101.4; MS (ESI) *m/z* 573.1; HRMS: calculado para $C_{34}H_{34}N_2O_5$ + H+, 551.25405; encontrado (ESI-FTMS, $[M+H]^{1+}$), 551.2538.

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Ejemplo 10F; N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-etinilbifenil-4-il)etil]-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-etinilbifenil-4-il)etil]-L-α-glutaminato

MS (ESI) *m/z* 587.3; MS (ESI) *m/z* 1173.5; HRMS: calculado para $C_{38}H_{38}N_2O_4$ + H+, 587.29043; encontrado (ESI-FTMS, $[M+H]^{1+}$), 587.29016.

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-etinilbifenil-4-il)etil]-L-α-glutamina

MS (ESI) *m/z* 529.2; HRMS: calculado para $C_{34}H_{30}N_2O_4$ + H+, 531.22783; encontrado (ESI- FTMS, $[M+H]^{1+}$), 531.22669.

Ejemplo 10G; N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-piridin-2-ilfenil)etil]-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-piridin-2-ilfenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 564.3; HRMS: calculado para $C_{35}H_{37}N_3O_4$ + H+, 564.28568; encontrado (ESI- FTMS, $[M+H]^{1+}$), 564.28472.

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-piridin-2-ilfenil)etil]-L-α-glutamina

MS (ESI) *m/z* 508.2.

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Ejemplo 10H; N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-piridin-4-ilfenil)etil]-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-piridin-4-ilfenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 564.2; HRMS: calculado para $C_{35}H_{37}N_3O_4$ + H+, 564.28568; encontrado (ESI- FTMS, $[M+H]^{1+}$), 564.28648.

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-piridin-4-ilfenil)etil]-L-α-glutamina

MS (ESI) *m/z* 508.1; MS (ESI) *m/z* 275.1; HRMS: calculado para $C_{31}H_{29}N_3O_4$ + H+, 508.22308; encontrado (ESI-FTMS, $[M+H]^{1+}$), 508.22403.

Ejemplo 10I: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(3-piridin-2-ilfenil)etil]-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(3-piridin-2-ilfenil)etil]-L-α-glutaminato

MS (ESI) *m/z* 564.3; HRMS: calculado para $C_{35}H_{37}N_3O_4$ + H+, 564.28568; encontrado (ESI- FTMS, $[MH-H]^{1+}$), 564.28531.

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(3-piridin-2-ilfenil)etil]-L-α-glutamina

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MS (ESI) *m/z* 508.1; HRMS: calculado para $C_{31}H_{29}N_3O_4$ + H+, 508.22308; encontrado (ESI- FTMS, $[M+H]^{1+}$), 508.22432.

Ejemplo 10J; N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-3-il)etil]-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-3-il)etil]-L-α-glutaminato

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-3-il)etil]-L-α-glutamina

MS (ESI) *m/z* 535.2; MS (ESI) *m/z* 1069.3; HRMS: calculado para $C_{33}H_{30}N_2O_5$ + H+, 535.22275; encontrado (ESI-FTMS, $[M+H]^{1+}$), 535.22147.

Ejemplo 10K; N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4'-(trifluorometil)bifenil-3-illetil)-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4'-(trifluorometil)bifenil-3-il]etil}-L-α-glutaminato

HRMS: calculado para $C_{37}H_{37}F_3N_2O_4$ + H+, 631.27782; encontrado (ESI-FTMS, $[M+H]^{1+}$), 631.27639.

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4'-(trifluorometil)bifenil-3-il]etil}-L-α-glutamina

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MS (ESI) *m/z* 575.2; HRMS: calculado para $C_{33}H_{29}F_3N_2O_4$ + H+, 575.21522; encontrado (ESI-FTMS, $[M+H]^{1+}$), 575.21382.

Ejemplo 10L: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-metoxibifenil-3-il)etil]-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-metoxibifenil-3-il)etil]-L-α-glutaminato

HRMS: calculado para $C_{37}H_{40}N_2O_5$ + H+, 593.30100; encontrado (ESI-FTMS, $[M+H]^{1+}$), 593.29993.

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-metoxibifenil-3-il)etil]-L-α-glutamina

MS (ESI) *m/z* 537.2; HRMS: calculado para $C_{33}H_{32}N_2O_5$ + H+, 537.23840; encontrado (ESI- FTMS, $[M+H]^{1+}$), 537.23745.

Ejemplo 10M: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-vinilbencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-vinilbencil)-L-α-glutaminato

Se utiliza *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-yodobencil)-L-α-glutaminato como el material de partida. MS (ESI) *m/z* 499.2; MS (ESI) *m/z* 997.4; HRMS: calculado para $C_{31}H_{34}N_2O_4$ + H+, 499.25913; encontrado (ESI-FTMS, $[M+H]^{1+}$), 499.25906.

Etapa B: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-vinilbencil)-L-α-glutamina

MS (ESI) *m/z* 443.2; MS (ESI) *m/z* 885.3; HRMS: calculado para $C_{27}H_{26}N_2O_4$ + H+, 443.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 443.19728.

Ejemplo 10N; N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-tien-2-ilbencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-tien-2-ilbencil)-L-α-glutaminato

Se utiliza *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-yodobencil)-L-α-glutaminato como el material de partida. MS (ESI) *m/z* 555.2; MS (ESI) *m/z* 1109.3; HRMS: calculado para $C_{33}H_{34}N_2O_4S$ + H+, 555.23120; encontrado (ESI-FTMS, $[M+H]^{1+}$), 555.23173.

Etapa B: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-tien-2-ilbencil)-L-α-glutamina

MS (ESI) *m/z* 499.1; HRMS: calculado para $C_{29}H_{26}N_2O_4S$ + H+, 499.16860; encontrado (ESI-FTMS, $[M+H]^{1+}$), 499.16976.

Ejemplo 10O: N^2-(bifenil-4-ilcarbonil-N^1-{[4'-(trifluorometil)bifenil-3-ilimetill-1-g-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil-N^1-{[4'-(trifluorometil)bifenil-3-il]metil}-L-α-glutaminato

Se utiliza *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-yodobencil)-L-α-glutaininate como el material de partida. MS (ESI) *m/z* 617.2; MS (ESI) *m/z* 1233.3; HRMS: calculado para $C_{36}H_{35}F_3N_2O_4$ + H+, 617.26217; encontrado (ESI-FTMS, $[M+H]^{1+}$), 617.26334.

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-{[4'-(trifluorometil)bifenil-3-il]metil}-L-α-glutamina

MS (ESI) *m/z* 559.1; MS (ESI) *m/z* 1119.1; HRMS: calculado para $C_{32}H_{27}F_3N_2O_4$ + H+, 561.19957; encontrado (ESI-FTMS, $[M+H]^{1+}$), 561.2001.

Ejemplo 10P: N^2-(bifenil-4-ilcarbonil)-N^1-[(4'-etinilbifenil-3-il)metil]-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-[(4'-etinilbifenil-3-il)metil]-L-α-glutaminato

Se utiliza *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-yodobencil)-L-α-glutaminato como el material de partida. MS (ESI) *m/z* 573.2; MS (ESI) *m/z* 1145.4; HRMS: calculado para $C_{37}H_{36}N_2O_4$ + H+, 573.27478; encontrado (ESI-FTMS, $[M+H]^{1+}$), 573.27518.

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Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-[(4'-etinilbifenil-3-il)metil]-L-α-glutamina

MS (ESI) *m/z* 517.2; MS (ESI) *m/z* 1033.3; HRMS: calculado para $C_{33}H_{28}N_2O_4$ + H+, 517.21218; encontrado (ESI-FTMS, $[M+H]^{1+}$), 517.2125.

Ejemplo 10Q: N^2-(bifenil-4-ilcarbonil)-N^1-(3-piridin-2-ilbencil)-L-α-glutamina

Etapa A: *terc*-butil N^2-(bifenil-4-ilcarbonil)-N^1-(3-piridin-2-ilbencil)-L-α-glutaminato

Se utiliza *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-yodobencil)-L-α-glutaminato como el material de partida. MS (ESI) *m/z* 550.2; HRMS: calculado para $C_{34}H_3SN_3O_4$ + H+, 550.27003; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 550.27066.

Etapa B: N^2-(bifenil-4-ilcarbonil)-N^1-(3-piridin-2-ilbencil)-L-α-glutamina

MS (ESI) *m/z* 494.1; HRMS: calculado para $C_{30}H_{27}N_3O_4$ + H+, 494.20743; encontrado (ESI- FTMS, $[M+H]^{1+}$), 494.20803.

Ejemplo 10R: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-vinilbencil)-L-α-glutamina

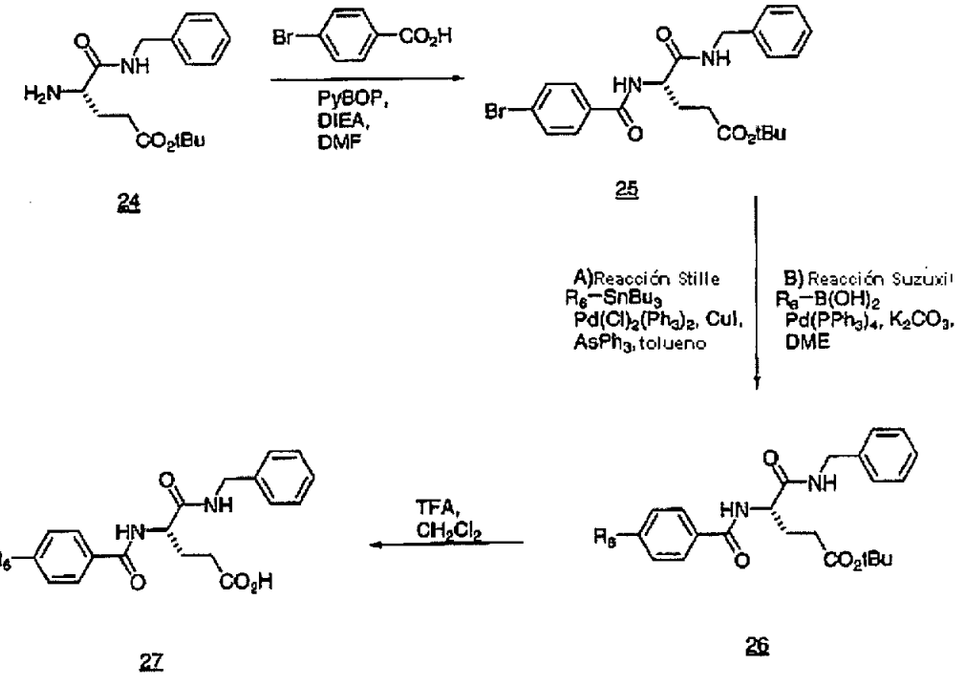
Etapa A: *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-vinilbencil)-L-α-glutaminato

Se utiliza *terc*-butil N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-yodobencil)-L-α-glutaininate como el material de partida. MS (ESI) *m/z* 499.2; MS (ESI) *m/z* 997.3; HRMS: calculado para $C_{3J}H_{34}N_2O_4$ + H+, 499.25913; encontrado (ESI-FTMS, $[M+H]^{1+}$), 499.25883.

Etapa B: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-vinilbencil)-L-α-glutamina

MS (ESI) *m/z* 443.1; HRMS: calculado para $C_{27}H_{26}N_2O_4$ + H+, 443.19653; encontrado (ESI- FTMS, $[M+H]^{1+}$), 443.19697.

Esquema 9



Ejemplo 11; N^1-bencil-N^2-(4-tien-2-ilbenzoil)-L-α-glutamina

Etapa A: *terc*-butil N^1-bencil-N^2-(4-bromobenzoil)-L-α-glutaminato

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Una solución de terc-butil éster de ácido 4-Amino-4-bencilcarbamoil-butírico (6.39 g, 21.9 mmol, 1 equiv.) en DMF (18 mL) se agrega a ácido 4-Bromobenzoico (4.39 g, 21.9 mmol, 1 equiv.) y PyBOP (14.7 g, 28.2 mmol, 1.2 equiv.) y la solución se agita a temperatura ambiente bajo nitrógeno. Luego se agrega en forma de gota DIEA (4.58 mL, 26.3 mmol, 1.2 equiv.) y la solución se agita durante 2 hrs. la reacción se completa como se determina mediante TLC. La solución se diluye con EtOAc (250 mL) y se lava consecutivamente con H_2O, 10% de HCl, $NaHCO_3$ satur., solución salina, y se seca sobre Na_2SO_4. Después el disolvente se evapora, el residuo crudo se disuelve en éter y se lava con LiBr ac. (2 x 250 mL) y se seca sobre Na_2SO_4. Un sólido tostado claro se obtiene, 8.94 g de *terc*-butil N^1-*bencil*-N^2-(4-bromobenzoil)-L-α-glutaminato en 86 % de rendimiento. MS (ESI) *m/z* 475.1; MS (ESI) *m/z* 949.2; HRMS: calculado para $C_{23}H_{27}BrN_2O_4$ + Na+, 497.10464; encontrado (ESI_FTMS, $[M+Na]^{1+}$), 497.10542.

Etapa B: *terc*-butil N^1-bencil-N^2-(4-tien-2-ilbenzoil)-L-α-glutaminato

Se disuelve *terc*-butil N^1-bencil-N^2-(4-bromobenzoil)-L-α-glutaminato (200 mg, 0.421 mmol) en tolueno (4 mL) bajo nitrógeno. Luego se agregan yoduro de cobre (16.0 mg, 0.0841 mmol), trifenilarsina (26.0 mg, 0.0841 mmol), y $Pd(Cl)_2(PPh_3)_2$ (59 mg, 0.0841 mmol) como sólidos. La mezcla de reacción luego se ajusta con un condensador y se calienta a reflujo (115° C), durante 10 minutos. Se agrega 2-

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(Tributilestanil)-tiofeno (267 mL, 0.841 mmol) e inmediatamente la reacción va de anaranjado a negro. Estas son condiciones típicas de la reacción. La reacción se monitorea por TLC y se completa en 30 minutos. La mezcla de reacción se filtra a través de celita y la celita se enjuaga con MeOH (1 mL). El disolvente se remueve y el residuo amarillo restante se disuelve en una cantidad mínima de CH_2Cl_2. Se agregan hexanos, precipitando en un sólido blanco que se filtra, se lava con hexanos, y luego se seca a presión reducida. 140 mg de *terc*-butil N^1-bencil-N^2-(4-tien-2-ilbenzoil)-L-α-glutaminato, un sólido blanco se obtiene en 69% de rendimiento. MS (ESI) *m/z* 479.1; MS (ESI) *m/z* 957.3; HRMS: calculado para $C_{27}H_{30}N_2O_4S$ + H+, 479.19990; encontrado (ESI_FT, $[M+H]^{1+}$), 479.19826.

Etapa C: N^1-bencil-N^2-(4-tien-2-ilbenzoil)-L-α-glutamina

Se disuelve *terc*-butil N^1-bencil-N^2-(4-tien-2-ilbenzoil)-L-α-glutaminato (135 mg, 0.282 mmol) en CH_2Cl_2 (1.5 mL) bajo nitrógeno. Se diluye TFA en CH_2Cl_2 (2 mL), y luego se agrega a la reacción. La reacción se monitorea por TLC y se completa en 2 hrs. El disolvente se remueve y el residuo amarillo restante se disuelve en tolueno, que luego se remueve (2x) dejando un sólido naranja. El sólido naranja se toma en acetona, y se agrega hexanos, precipitando un sólido naranja pálido. El sólido se filtra, se lava con hexanos, y se seca a presión reducida. El sólido naranja pálido se corre en una columna de SiO_2, utilizando 4% de MeOH/CH_2Cl_2. El disolvente se remueve a partir de las fracciones produciendo 79 mg de

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N^1-bencil-N^2-(4-tien-2-ilbenzoil)-L-α-glutamina, un sólido blanco, en 66% de rendimiento. MS (ESI) *m/z* 421.1; MS (ESI) *m/z* 843.3; HRMS: calculado para $C_{23}H_{22}N_2O_4S$ + H+, 423.13730; encontrado (ESI_FTMS, $[M+H]^{1+}$), 423.13742.

Ejemplo 12:

Los siguientes compuestos se preparan de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 11.

Ejemplo 12A; N^1-bencil-N^2-[4-(2-furil)benzoil]-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-[4-(2-furil)benzoil]-L-α-glutaminato

MS (ESI) *m/z* 463.2; MS (ESI) *m/z* 925.3; HRMS: calculado para $C_{27}H_{30}N_2O_5$ + H+, 463.22275; encontrado (ESI_FT, $[M+H]^{1+}$), 463.22159.

Etapa C: N^1-bencil-N^2-[4-(2-furil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 407.1; MS (ESI) *m/z* 813.2; HRMS: calculado para $C_{23}H_{22}N_2O_5$ + H+, 407.16015; encontrado (ESI_FTMS, $[M+H]^{1+}$), 407.16031.

Ejemplo 12B: N^1-bencil-N^2-[(4'-etinil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

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Etapa B: *terc*-butil N^1-bencil-N^2-[(4'-etinil-1,1-bifenil-4-il)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 497.3; MS (ESI) *m/z* 993.5; HRMS: calculado para $C_{31}H_{32}N_2O_4$ + H+, 497.24348; encontrado (ESI_FTMS, $[M+H]^{1+}$), 497.24306.

Etapa C: N^1-bencil-N^2-[(4'-etinil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 439.2; MS (ESI) *m/z* 879.4; HRMS: calculado para $C_{27}H_{24}N_2O_4$ + H+, 441.18088; encontrado (ESI_FT, $[M+H]^{1+}$), 441.18056.

Ejemplo 12C: N^1-bencil-N^2-(4-piridin-3-ilbenzoil)-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-(4-piridin-3-ilbenzoil)-L-α-glutaminato

MS (ESI) *m/z* 474.2; HRMS: calculado para $C_{28}H_{31}N_3O_4$ + H+, 474.23873; encontrado (ESI_FT, $[M-HH]^{1+}$), 474.238741.

Etapa C: N^1-bencil-N^2-(4-piridin-3-ilbenzoil)-L-α-glutamina

MS (ESI) *m/z* 418.1; HRMS: calculado para $C_{24}H_{23}N_3O_4$ + H+, 418.17613; encontrado (ESI_FT, $[M+H]^{1+}$), 418.17555.

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Ejemplo 12D: N^1-bencil-N^2-[4-(1,3-tiazol-2-il)benzoil]-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-[4-(1,3-tiazol-2-il)benzoil]-L-α-glutaminato

MS (ESI) *m/z* 480.2; MS (ESI) *m/z* 959.2; HRMS: calculado para $C_{26}H_{29}N_3O_4S$ + H+, 480.19515; encontrado (ESI_FT, $[M+H]^{1+}$), 480.19659.

Etapa C: N^1-bencil-N^2-[4-(1,3-tiazol-2-il)benzoil]-L-α-glutamina

MS (ESI) *m/z* 422.2; MS (ESI) *m/z* 845.3; HRMS: calculado para $C_{22}H_{21}N_3O_4S$ + H+, 424.13255; encontrado (ESI_FT, $[M+H]^{1+}$), 424.13204.

Ejemplo 12E: N^1-bencil-N^2-(4-piridin-2-ilbenzoil)-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-(4-piridin-2-ilbenzoil)-L-α-glutaminato

MS (ESI) *m/z* 474.2; HRMS: calculado para $C_{28}H_{31}N_3O_4$ + H+, 474.23873; encontrado (ESI_FT, $[MH-H]^{1+}$), 474.2401.

Etapa C: N^1-bencil-N^2-(4-piridin-2-ilbenzoil)-L-α-glutamina

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MS (ESI) *m/z* 418.1; HRMS: calculado para $C_{24}H_{23}N_3O_4$ + H+, 418.17613; encontrado (ESI_FT, $[M+H]^{1+}$), 418.17517.

Ejemplo 12F: *N*-bencil-N^2-[4-(2-naftil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 467.2; MS (ESI) *m/z* 933.4; HRMS: calculado para $C_{29}H_{26}N_2O_4$ +H+, 467.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 467.19661.

Ejemplo 12G; *N*-bencil-N^2-[4-(feniletinil)benzoil]-L-α-glutamina

MS (ESI) *m/z* 441.2; MS (ESI) *m/z* 881.4.

Ejemplo 12H: N-bencil-N^2-[4-(9-hidroxi-9*H*-fluoren-9-il)etinil]benzoil}-L-α-glutamina

MS (ESI) *m/z* 543.1; MS (ESI) *m/z* 1087.2.

Ejemplo 12I: *N*-bencil-N^2-{4-[(1E)-3-oxo-3-fenilprop-1-en-1-il]benzoill-L-α-glutamina

MS (ESI) *m/z* 471.2; MS (ESI) *m/z* 941.4.

Ejemplo 12J: N^2-{4-[(3-aminofenil)etinil]benzoil}-*N*-bencil-L-α-glutamina

MS (ESI) *m/z* 456.1; MS (ESI) *m/z* 249.1.

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Ejemplo 12K: *N*-bencil-N^2-[4-(3-hidroxi-3,3-difenilprop-1-in-1-il)benzoil]-L-α-glutamina

MS (ESI) *m/z* 545.1; MS (ESI) *m/z* 1091.2; MS (ESI) *m/z* 659.1.

Ejemplo 12L: *N*-bencil-N^2-{4-[(3-metoxifenil)etinil]benzoil}-L-α-glutamina

MS (ESI) *m/z* 471.1; MS (ESI) *m/z* 941.2.

Ejemplo 13:

Los siguientes compuestos se preparan de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 11, excepto que una reacción Suzuki en la etapa B en lugar de una reacción Stille. La hidrólisis del éster al producto final siguiendo el mismo procedimiento como se describió previamente

Ejemplo 13A: N^1-bencil-N^2-[(3',5'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-[(3',5'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato

Se disuelve *terc-butil* N^1-bencil-N^2-(4-bromobenzoil)-L-α-glutaminato (350 mg, 0.736 mmol) en DME, bajo nitrógeno en un frasco sellado. Se agregan ácido 3,5-Dimetilborónico (110 mg, 0.736 mmol), y $Pd(PPh_3)_4$ (43 mg, 0.037 mmol) como sólidos,

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y la reacción se calienta a reflujo durante 10 minutos. En este punto se agrega K_2CO_3 2M (735 mL, 1.47 mmol), el frasco de reacción se sella, y la reacción se calienta a reflujo y se monitorea por TLC. La reacción se completa en 2 hrs. La parte acuosa de la reacción se remueve por vía de pipeta. La solución de reacción luego se filtra a través de celita y la celita se enjuaga con MeOH. El disolvente se remueve, dejando un sólido café. El producto se purifica utilizando una columna SiO_2 y 33% de EtOAc/Hex como el disolvente. El producto se obtiene como un sólido blanco, produciendo 222 mg a 60% de rendimiento. MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.6; HRMS: calculado para $C_{31}H_{36}N_2O_4$ + H+, 501.27478; encontrado (ESI_FT, $[MH-H]^{1+}$), 501.27332.

Etapa C: N^1-bencil-N^2-[(3',5'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

MS (ESI_FT) *m/z* 445.21151; MS (ESI_FT) *m/z* 445.21219; HRMS: calculado para $C_{27}H_{28}N_2O_4$ + H+, 445.21218; encontrado (ESI_FT, $[M+H]^{1+}$), 445.21151.

Ejemplo 13B: N^1-bencil-N^2-[(2',5'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-[(2',5'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato

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MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.6; HRMS: calculado para $C_{31}H_{36}N_2O_4$ + H+, 501.27478; encontrado (ESI_FT, $[M+H]^{1+}$), 501.27441.

Etapa C: N^1-bencil-N^2-[(2',5'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 445.3; MS (ESI) *m/z* 889.5; HRMS: calculado para $C_{27}H_{28}N_2O_4$ + H+, 445.21218; encontrado (ESI_FT, $[M+H]^{1+}$), 445.21172.

Ejemplo 13C: N^1-bencil-N^2-[(4'-etil-1,1'-bifenil-4-il)carbonil]-1-a-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-[(4^1-etil-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.6; HRMS: calculado para $C_{31}H_{36}N_2O_4$ + H+, 501.27478; encontrado (ESI_FT, $[M+H]^{1+}$), 501.27326.

Etapa C: N^1-bencil-N^2-[(4'-etil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

MS (ESLFT) *m/z* 445.2115; MS (ESI_FT) *m/z* 445.21219; HRMS: calculado para $C_{27}H_{28}N_2O_4$ + H+, 445.21218; encontrado (ESI_FT, $[M+H]^{1+}$), 445.2115.

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Ejemplo 13D: N^1-bencil-N^2-[(3'-etoxi-1,1'-bifenil-4-ilcarbonill-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-[(3'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1033.6; HRMS: calculado para $C_{31}H_{36}N_2O_5$ + H+, 517.26970; encontrado (ESI_FT, $[M+H]^{1+}$), 517.26837.

Etapa C: N^1-bencil-N^2-[(3'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

MS (ESI_FT) *m/z* 461.20568; MS (ESI_FT) *m/z* 461.2071; HRMS: calculado para $C_{27}H_{28}N_2O_5$ +H+, 461.20710; encontrado (ESI_FT, $[M+H]^{1+}$), 461.20568.

Ejemplo 13E: N^1-bencil-N^2-[(2'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-[(2'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 517.3; MS (ESI) *m/z* 1033.5; HRMS: calculado para $C_{31}H_{36}N_2O_5$ + H+, 517.26970; encontrado (ESI_FT, $[M+H]^{1+}$), 517.26833.

Etapa C: N^1-bencil-N^2-[(2'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

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MS (ESI_FT) *m/z* 461.20572; MS (ESI_FT) *m/z* 461.2071; HRMS: calculado para $C_{27}H_{28}N_2O_5$ +H+, 461.20710; encontrado (ESI_FT, $[M+H]^{1+}$), 461.20572.

Ejemplo 13F; N^1-bencil-N^2-[(2',6'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-[(2',6'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato

MS (ESI_FT) *m/z* 501.27323; MS (ESI_FT) *m/z* 501.27479; HRMS: calculado para $C_{31}H_{36}N_2O_4$ + H+, 501.27478; encontrado (ESI_FT, $[M+H]^{1+}$), 501.27323.

Etapa C: N^1-bencil-N^2-[(2',6'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

MS (ESI_FT) *m/z* 445.21145; MS (ESI_FT) *m/z* 445.21219; HRMS: calculado para $C_{27}H_{28}N_2O_4$ + H+, 445.21218; encontrado (ESI_FT, $[M+H]^{1+}$), 445.21145.

Ejemplo 13G: N^1-bencil-N^2-[(4'-vinil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-[(4'-vinil-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato

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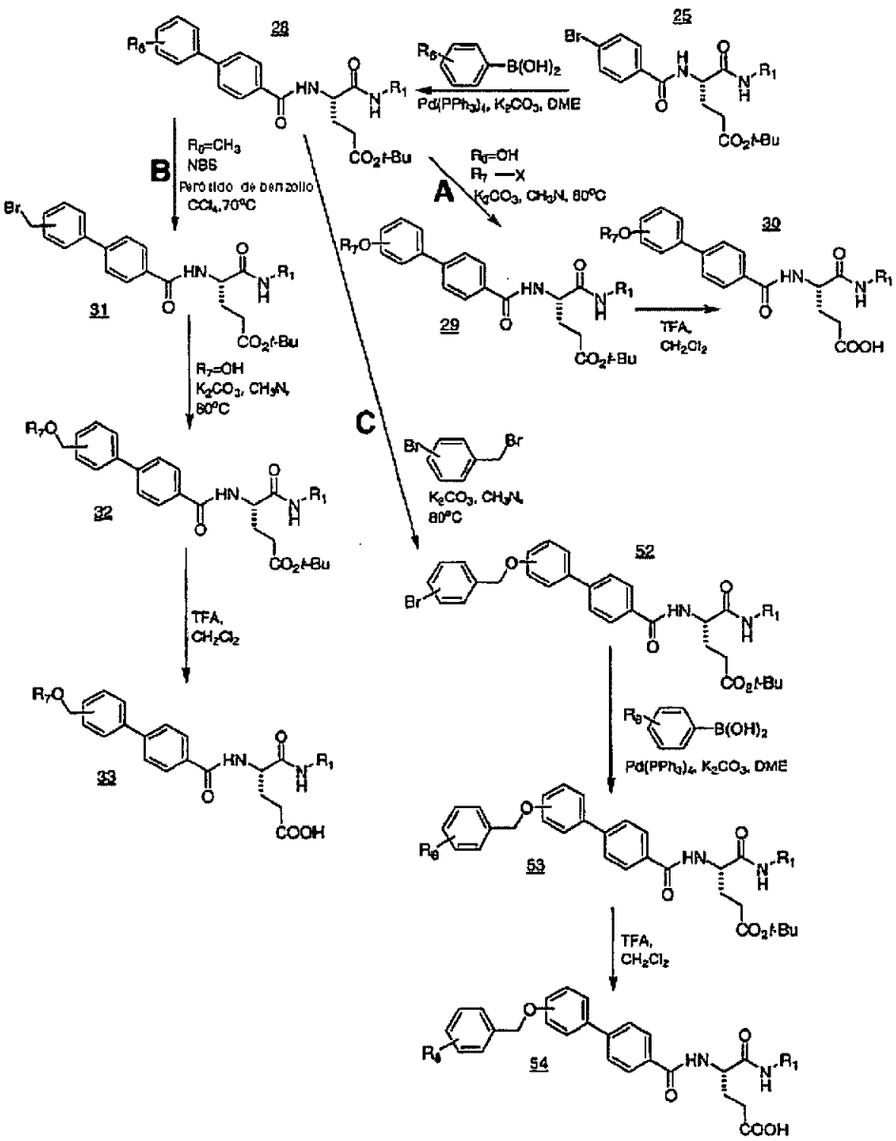
MS (ESI) *m/z* 499.3; MS (ESI) *m/z* 997.5; HRMS: calculado para $C_{31}H_{34}N_2O_4$ + H+, 499.25913; encontrado (ESI_FT, $[M+H]^{1+}$), 499.25855.

Etapa C: N^1-bencil-N^2-[(4'-vinil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 443.2; MS (ESI) *m/z* 885.4; HRMS: calculado para $C_{27}H_{26}N_2O_4$ + H+, 443.19653; encontrado (ESI-FTMS, $[M+H]^{1+}$), 443.19675.

Esquema 10



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Ejemplo 14: N^1-bencil-N^2-[(4'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

Etapa A: *terc*-butil N^1-bencil-N^2-[(4'-hidroxi-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato

Se disuelve *terc*-butil N^1-bencil-N^2-(4-bromobenzoil)-L-α-glutaminato (3.00g,6.31 mmol) en DME (40 mL), bajo nitrógeno en un frasco bomba de 75 mL. Se agregan ácido 4-hidroxifenilborónico (871 mg, 6.31 mmol), y $Pd(PPh_3)_4$ (729 mg, 0.631 mmol) como sólidos, y la reacción se calienta a reflujo durante 30 minutos. En este punto se disuelve K_2CO_3 (1.74 g, 12.6 mmol) en H_2O (8 mL), y se agrega a la reacción. El frasco bomba se sella y la reacción se calienta a reflujo, se agita durante la noche, y se monitorea por TLC. La reacción se completa después de agitar durante la noche. La mezcla de reacción se filtra a través de celita y la celita se enjuaga con MeOH. El disolvente se remueve y el sólido restante se disuelve en EtOAc (200 mL) y luego se lava con 200 mL de 10% de HCl (2x) y solución salina. La capa orgánica (superior) luego se seca (Na_2SO_4), se filtra y se concentra, dejando un sólido aceitoso rojo oscuro. El producto se purifica utilizando una columna SiO_2, y 40% de Ace/Hex como el disolvente. Este no se disolvería en este disolvente de tal manera que se disuelve en Acetona/MeOH (1:1) y se seca montado en la columna. El producto se obtiene como el tercer punto de la columna y como un sólido amarillo. Rendimiento 1.9 g de *terc*-butil N^1-bencil-N^2-[(4'-hidroxi-1,1'-bifenil-4-

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il)carbonil]-L-α-glutaminato en 62% de rendimiento. MS (ESI) *m/z* 487.4; MS (ESI) *m/z* 533.5; MS (ESI) *m/z* 975.8; HRMS: calculado para $C_{29}H_{32}N_2O_5$ + H+, 489.23840; encontrado (ESI_FTMS, $[MH-H]^{1+}$), 489.23862.

Etapa B: *terc*-butil N^1-bencil-N^2-[(4'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato

Se disuelve *terc*-butil N^1-bencil-N^2-[(4'-hidroxi-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato (300 mg, 0.614 mmol) en CH_3CN (7 mL) en un frasco sellado 20 mL. Se agrega K_2CO_3 como un sólido, el frasco sellado y se calienta a 80° C durante 1 hora. Se agrega yodoetano (54 mL, 0.675 mmol), el frasco sellado y se agita a 80° C durante la noche. La reacción se monitorea por TLC y se completa después de agitar durante la noche. El disolvente se remueve por vía de soplador de nitrógeno, y el sólido restante se disuelve en CH_2Cl_2 (7 mL) y se lava con 10% HCl (7 mL). La capa acuosa se decanta con una pipeta, y el disolvente se remueve por vía de soplador de nitrógeno. El sólido restante se disuelve en DMSO (2 mL) y se purifica en un HPLC Gilson. Rendimiento: 123 mg de *terc*-butil N^1-bencil-N^2-[(4'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato, un sólido blanco en 39% de rendimiento. MS (ESI) *m/z* 517.2; MS (ESI) *m/z* 1033.4; HRMS: calculado para $C_{31}H_{36}N_2O_5$ + H+, 517.26970; encontrado (ESI_FTMS, $[M+H]^{1+}$), 517.26801.

Etapa C: N^1-bencil-N^2-[(4'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

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El procedimiento utilizado es similar a aquel descrito en el Ejemplo 13. MS (ESI) *m/z* 461.2; MS (ESI) *m/z* 921.4; HRMS: calculado para $C_{27}H_{28}N_2O_5$ + H+, 461.20710; encontrado (ESI_FTMS, $[M+H]^{1+}$), 461.20542.

Ejemplo 15:

Los siguientes compuestos se preparan de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 14.

Ejemplo 15A: N^1-bencil-N^2-[(4'-propoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-[(4'-propoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 531.3; MS (ESI) *m/z* 1061.4; HRMS: calculado para $C_{32}H_{38}N_2O_5$ + H+, 531.28535; encontrado (ESI_FTMS, $[M+H]^{1+}$), 531.2844.

Etapa C: N^1-bencil-N^2-[(4'-propoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 4152; MS (ESI) *m/z* 949.4; HRMS: calculado para $C_{28}H_{30}N_2O_5$ + H+, 475.22275; encontrado (ESI_FTMS, $[M+H]^{1+}$), 475.22333.

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Ejemplo 15B: N^1-bencil-N^2-[(4'-butoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-[(4'-butoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 545.3; MS (ESI) *m/z* 1089.5; HRMS: calculado para $C_{33}H_{40}N_2O_5$ + H+, 545.30100; encontrado (ESI_FTMS, $[M+H]^{1+}$), 545.30048.

Etapa C: N^1-bencil-N^2-[(4'-butoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 489.3; MS (ESI) *m/z* 977.4; HRMS: calculado para $C_{29}H_{32}N_2O_5$ + H+, 489.23840; encontrado (ESLFTMS, $[M+H]^{1+}$), 489.23871.

Ejemplo 15C: N^1-bencil-N^2-{[4'(ciclobutil)metoxi)-1,1'-bifenil-4-il)carbonil}-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-{[4'(ciclobutilmetoxi)-1,1'-bifenil-4-il)carbonil}-L-α-glutaminato

MS (ESI) *m/z* 557.3; MS (ESI) *m/z* 1113.4; HRMS: calculado para $C_{34}H_{40}N_2O_5$ + H+, 557.30100; encontrado (ESI_FTMS, $[M+H]^{1+}$), 557.30064.

Etapa C: N^1-bencil-N^2-{[4'-(ciclobutilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina

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MS (ESI) *m/z* 501.3; MS (ESI) *m/z* 1001.5; HRMS: calculado para $C_{30}H_{32}N_2O_5$ + H+, 501.23840; encontrado (ESI_FTMS, $[M+H]^{1+}$), 501.23937.

Ejemplo 15D: *terc*-butil N^1-bencil-N^2-{[4'(ciclohexilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-{[4'-(ciclohexilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutaminato

MS (ESI) *m/z* 585.3; MS (ESI) *m/z* 1169.5; HRMS: calculado para $C_{36}H_{44}N_2O_5$ + H+, 585.33230; encontrado (ESI_FTMS, $[M+H]^{1+}$), 585.33275.

Etapa C: N^1-bencil-N^2-{[4'-(ciclohexilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina

MS (ESI) *m/z* 529.3; MS (ESI) *m/z* 1057.5; HRMS: calculado para $C_{32}H_{36}N_2O_5$ + H+, 529.26970; encontrado (ESI_FTMS, $[M+H]^{1+}$), 529.27022.

Ejemplo 15E: N^2-{[4'-(aliloxi)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutamina

Etapa B: *terc*-butil N^2-{[4'-(aliloxi)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutaminato

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MS (ESI) *m/z* 529.2; MS (ESI) *m/z* 1057.4; HRMS: calculado para $C_{32}H_{36}N_2O_5$ + H+, 529.26970; encontrado (ESI_FTMS, $[M+H]^{1+}$), 529.26804.

Etapa C: N^2-{[4'-(aliloxi)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutamina

Ejemplo 15F: N^1-bencil-N^2-({4'-[(3-metoxibenil)oxi]-1,1'-bifenil-4-il}carbonil)-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-({4'-[(3-metoxibencil)oxi]-1,1'-bifenil-4-il}carbonil)-L-α-glutaminato

MS (ESI) *m/z* 609.3; MS (ESI) *m/z* 1217.5; HRMS: calculado para $C_{37}H_{40}N_2O_6$ + H+, 609.29591; encontrado (ESI-FTMS, $[M+H]^{1+}$), 609.29669..

Etapa C: N^1-bencil-N^2-({4'-[(3-metoxibencil)oxi]-1,1'-bifenil-4-il}carbonil)-L-α-glutamina

MS (ESI) *m/z* 553.2; MS (ESI) *m/z* 1105.3; HRMS: calculado para $C_{33}H_{32}N_2O_6$ + H+, 553.23331; encontrado (ESI-FTMS, $[M+H]^{1+}$), 553.23235.

Ejemplo 15G: N^1-bencil-N^2-({4'-[(3,5-dimetoxibencil)oxi]-1,1'-bifenil-4-il}carbonil)-L-α-glutamina

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Etapa B: *terc*-butil N^1-bencil-N^2-({4'-[(3,5-dimetoxibencil)oxi]-1,1'-bifenil-4-il}carbonil)-L-α-glutaminato

MS (ESI) *m/z* 639.3; MS (ESI) *m/z* 1277.4; HRMS: calculado para $C_{38}H_{42}N_2O_7$ + H+, 639.30648; encontrado (ESI-FTMS, $[M+H]^{1+}$), 639.30698.

Etapa C: N^1-bencil-N^2-({4'-[(3,5-dimetoxibencil)oxi]-1,1'-bifenil-4-il}carbonil)-L-α-glutamina

MS (ESI) *m/z* 583.2; MS (ESI) *m/z* 1165.3; HRMS: calculado para $C_{34}H_{34}N_2O_7$ + H+, 583.24388; encontrado (ESI-FTMS, $[M+H]^{1+}$), 583.2433.

Ejemplo 15H: N^1-bencil-N^2-{[4'-(2-naftilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-{[4'-(2-naftilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutaminato

MS (ESI) *m/z* 629.3; HRMS: calculado para $C_{40}H_{40}N_2O_5$ + H+, 629.30100; encontrado (ESI- FTMS, $[M+H]^{1+}$), 629.30277.

Etapa C: N^1-bencil-N^2-{[4'-(2-naftilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina

MS (ESI) *m/z* 571.3; HRMS: calculado para $C_{36}H_{32}N_2O_5$ + H+, 573.23840; encontrado (ESI- FTMS, $[M+H]^{1+}$), 573.23779.

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Ejemplo 15I: *N*-bencil-N^2-({4'-[(3-fluorobencil)oxi]bifenil-4-il}carbonil)-L-α-glutamina

MS (ESI) *m/z* 541.1; MS (ESI) *m/z* 1081.2.

Ejemplo 15J: *N*-bencil-N^2-{[4'-(benciloxi)bifenil-4-il]carbonil)-L-α-glutamina

MS (ESI) *m/z* 523.1; MS (ESI) *m/z* 1045.2.

Los siguientes compuestos se preparan de acuerdo con el Esquema 10, Ruta A:

Ejemplo 15K: N^2-1[3'-(benciloxi)bifenil-4-il]carbonil}-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 613.1; MS (ESI) *m/z* 1225.1; HRMS: calculado para $C_{35}H_{36}N_2O_8$ +H+, 613.25444; encontrado (ESI-FTMS, $[M+H]^{1+}$), 613.25451.

Ejemplo 15L: N^2-α3'-[(3,5-dimetoxibencil)oxi1bifenil-4-ilTcarbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 673.3; MS (ESI) *m/z* 1345.6; MS (ESI) *m/z* 690.4; HRMS: calculado para $C_{37}H_{40}N_2O_{10}$ + H+, 673.27557; encontrado (ESI-FTMS, $[M+H]^{1+}$), 673.27431.

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Ejemplo 15M: N^2-({3'-[(3-metoxibencil)oxi]bifenil-4-il}carbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 643.3; MS (ESI) *m/z* 1285.6; HRMS: calculado para $C_{36}H_{38}N_2O_9$ + H+, 643.26501; encontrado (ESI-FTMS, $[M+H]^{1+}$), 643.26574.

Ejemplo 15N: N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-*N*-[2-(4-fluorofenil)-1,1-dimetiletil1-L-α-glutamina

MS (ESI) *m/z* 643.3; MS (ESI) *m/z* 1285.6; HRMS: calculado para $C_{37}H_{39}FN_2O_7$ + H+, 643.28141; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 643.28187.

Los siguientes compuestos se preparan de acuerdo con el Esquema 10, Ruta B:

Ejemplo 15O: N^2-[(4'-{[3,5-bis(trifluorometil)fenoxi]metil}bifenil-4-il)carbonil1-*N*-(1,1-diinetil-2-feniletil)-L-α-glutamina

Etapa A: *terc*-butil *N*-(1,1-dimetil-2-feniletil)-N^2-[(4'-metilbifenil-4-il)carbonil]-L-α-glutaminato

Se disuelve *terc*-butil N^1-bencil-N^2-(4-bromobenzoil)-L-α-glutaminato (1.00 g, 1.93 mmol) en DME (10 mL) bajo nitrógeno y se coloca en un frasco de microondas. A- metilfenil boronic acid (526 mg, 3.87. mmol), y $Pd(PPh_3)_4$ (334 mg, 0.290 mmol) se

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agregan como sólidos antes de la adición de K_2CO_3 (800 mg, 5.79 mmol) se disuelve en H_2O (2.3 mL). El frasco se sella y se calienta a 800° C en un microndas durante 20 minutos. El disolvente se remueve y el aceite amarillo restante se disuelve en dietil éter (125 mL). The organics were washed consecutivamente con 10% HCl (125 mL), agua (125 mL) y solución salina (125 mL). La capa orgánica se seca con $MgSO_4$, se filtra a través de celita y el disolvente se remueve. El sólido pegajoso se purifica utilizando en una columna flash Combi 40 g utilizando un gradiente de incremento de EtOAc/Hex como el disolvente. El producto se obtiene como un sólido marrón claro. Rendimiento 792 mg de *terc*-butil *N*-(1,1-dimetil-2- feniletil)-N^2-[(4'-metilbifenil-4-il)carbonil]-L-α-glutaminato at 78% de rendimiento. MS (ESI) *m/z* 529.3; HRMS: calculado para $C_{33}H_{40}N_2O_4$ + H+, 529.30608; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 529.30594.

Etapa B: *terc*-butil N^2-{[4'-(bromometil)bifenil-4-il]carbonil}-*N*-(1,1-dimetil-2-feniletil)-L-α-glutaminato

Se disuelve *terc*-butil *N*-(1,1-dimetil-2-feniletil)-N^2-[(4'-metilbifenil-4-il)carbonil]-L-α-glutaminato (3.5 g, 6.62 mmol) en CCl_4 (50 mL) junto con *N*- Bromosuccinimida (2.36 g, 13.2 mmol) y peróxido de benzoilo (321 mg, 1.32 mmol) en un frasco de 100 mL equipado con un condensador de reflujo. La mezcla de reacción se agita durante la noche a 70° C. El disolvente se remueve y el residuo se purifica utilizando una columna SiO_2 y 20% de EtOAc/Hex como el disolvente dando un sólido amarillo. Rendimiento 1.05 g de *terc*-butil N^2-{[4'-

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(bromometil)bifenil-4-il]carbonil}-*N*-(1,1-dimetil-2-feniletil)-L-α-glutaminato en 57% de rendimiento. MS (ESI) *m/z* 607.1; HRMS: calculado para $C_{33}H_{39}BrN_2O_4$ + H+, 607.21660; encontrado (ESI-FTMS, $[M+H]^{1+}$), 607.21591.

Etapa C: *terc*-butil N^2-[(4'-{[3,5-bis(trifluorometil)fenoxi]metil}bifenil-4-il-carbonil]-*N*-(1,1-dimetil-1-feniletil)-L-α-glutaminato

terc-butil N^2-{[4'-(bromometil)bifenil-4-il]carbonil}-*N*-(1,1-dimetil-2- feniletil)-L-α-glutaminato (253 mg,041 mmol) 3,5-bis(trifluorometil)fenol (63 μL,.42 mmol) y K_2CO_3 (287 mg, 2.08 mmol) se combinan todos en un frasco de 10 mL. Se agrega acetonitrilo (4 mL) disolviendo algunos de los sólidos hasta que se calienta a 80° C. la reacción se monitorea utilizando TLC y MS. La reacción se agita durante la noche (18h). La reacción se filtra utilizando un embudo sinterizado y el disolvente se remueve. El filtrado se recolecta y el disolvente se remueve. El residuo se purifica utilizando una columna SiO_2 y 20% de EtOAc/Hex como el disolvente dando un sólido blanco. Rendimiento 242 mg de *terc*- butil N^2-[(4'-{[3,5-bis(trifluorometil)fenoxi]metil}bifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutaminato en 77% de rendimiento. MS (ESI) *m/z* 757.4 HRMS: calculado para $C_{41}H_{42}F_6N_2O_5$ + H+, 757.30707; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 757.30532.

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Etapa D: N^2-[(4'-{[3,5-bis(trifluorometil)fenoxi]metil}bifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

Se disuelve *terc*-butil N^2-[(4'-{[3,5-bis(trifluorometil)fenoxi]metil}bifenil-4-il)carbonil]-*N*-(*1,1*-dimetil-2-feniletil)-L-α-glutaminato (215 mg, 0.284 mmol) en CH_2Cl_2 (3 mL) y se agita en un frasco de 10 mL. Se agrega ácido trifluoroacético (1.09 mL, 14 mmol) y la solución se agita durante 2 horas. El disolvente se remueve y se seca bajo vacío. El residuo resultante se purifica utilizando HPLC preparativo (ACN/H_2O, 0.02% de TFA). Las fracciones pico principales se recolectan y después que se remueven del disolvente da el producto como un sólido blanco. Rendimiento de 104 mg de N^2-[(4'-{[3,5-bis(trifluorometil)fenoxi]metil}bifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina se obtiene en 52% de rendimiento. MS (ESI) *m/z* 699.3; HRMS: calculado para $C_{37}H_{34}F_6N_2O_5$ + H+, 701.24447; encontrado (ESI-FTMS, $[M+H]^{1+}$), 701.24429.

Los siguientes compuestos se preparan de acuerdo con el procedimiento descrito anteriormente por ejemplo 150:

Ejemplo 15P: N^2-({4'-[(1,3-benzodioxol-5-iloxi)metil]bifenil-4-il}carbonil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 609.3; MS (ESI) *m/z* 1217.6; HRMS: calculado para $C_{36}H_{36}N_2O_7$ + H+, 609.25953; encontrado (ESI-FTMS, $[M+H]^{1+}$), 609.26109.

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Ejemplo 15Q: N^2-({4'-[(3,5-dimetoxifenoxi)metil]bifenil-4-il}carbonil)-*N*-(3-metilbencil)-L-α-glutamina

MS (ESI) *m/z* 595.4; HRMS: calculado para $C_{35}H_{36}N_2O_7$ + H+, 597.25953; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 597.25901.

Ejemplo 15R: N^2-({3'-[(3,5-dimetoxifenoxi)metil]bifenil-4-il}carbonil)-*N*-(3-metilbenci)-L-α-glutamina

MS (ESI) *m/z* 595.2; HRMS: calculado para $C_{35}H_{36}N_2O_7$ + H+, 597.25953; encontrado (ESI-FTMS, $[M+H]^{1+}$), 597.2593.

Ejemplo 15S: N^2-[(3'-{[3,5-bis(trifluorometil)fenoxi1methvUbifenil-4-il)carbonil]-*N*-(3-metilbencil)-L-α-glutamina

MS (ESI) *m/z* 671.2; MS (ESI) *m/z* 1343.7; HRMS: calculado para $C_{35}H_{30}F_6N_2O_5$ + H+, 673.21317; encontrado (ESI-FTMS, $[M+H]^{1+}$), 673.21279.

Ejemplo 15T: N^2-({3'-[(3-etilfenoxi)metil]bifenil-4-il}carbonil)-*N*-(3-metilbencil)-L-α-glutamina

MS (ESI) *m/z* 563.3; HRMS: calculado para $C_{35}H_{36}N_2O_5$ + H+, 565.26970; encontrado (ESI-FTMS, $[M+H]^{1+}$), 565.26999.

Los siguientes compuestos se preparan de acuerdo con el Esquema 10, Ruta C:

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Ejemplo 15U: *N*-bencil-N^2-{[4'-(bifenil-3-ilmetoxi)bifenil-4-il]carbonil}-L-α-glutamina

Etapa A: terc-butil N^1-bencil-N^2-[(4'-hidroxi-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato

Se disuelve *terc*-butil N^1-bencil-N^2-(4-bromobenzoil)-L-α-glutaminato (2.00 g,4.21 mmol) en DME (20 mL) bajo nitrógeno y se coloca en un frasco de 75 mL. Se agregan ácido 4-Hidroxifenil borónico (638 mg, 4.63. mmol), y $Pd(PPh_3)_4$ (729 mg, 0.632 mmol) como sólidos antes de la adición de K_2CO_3 (1.75 g, 12.6 mmol) se disuelve en H_2O (5 mL). El frasco se sella y la reacción se calienta a reflujo, se agita durante dos días y se monitorea por TLC. La mezcla de reacción se filtra a través de celita y luego se enjuaga con MeOH. El disolvente se remueve y el residuo resultante se purifica utilizando una columna SiO_2 y 33% de EtOAc/Hex como el disolvente. El producto se obtiene como un sólido blanco. Rendimiento: 514 mg de *terc*-butil N^1-bencil-N^2-[(4'-hidroxi-1,1'-bifenil-4-il)carbonil]-L-α-glutaminato en 25% de rendimiento. MS (ESI) *m/z* 487.4; HRMS: calculado para $C_{29}H_{32}N_2O_5$ + H+, 489.23840; encontrado (ESI_FTMS, $[MH-H]^{1+}$), 489.23862.

Etapa B: *terc*-butil *N*-bencil-N^2-({4'-[(3-bromobencil)oxi]bifenil-4-il}carbonil)-L-α-glutaminato

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3,3-bromobencilbromuro y K_2CO_3 se combinan todos en un frasco de 20 mL. Se agrega CH_3CN (6 mL), disolviendo algunos de los sólidos hasta que se calienta a 80° C. La reacción se monitorea utilizando TLC y MS. Después de 2 horas la reacción se completa. El producto resultante se precipita rápidamente luego de enfriamiento del CH_3CN. La reacción se filtra utilizando un embudo sinterizado y el filtrado se recolecta y se redisuelve en CH_3CN caliente. La solución se le permite cristalizar durante la noche en el congelador. El sólido blanco se recolecta y se lava con CH_3CN frío. Rendimiento: 357 mg de *terc*-butil *N*-bencil-N^2-({4'-[(3-bromobencil)oxi]bifenil-4-il}carbonil)-L-α-glutaminato en 57% de rendimiento. MS (ESI) *m/z* 657.2.

Etapa C: *terc*-butil *N*-bencil-N^2-{[4'-(bifenil-3-ilmetoxi)bifenil-4-il]carbonil}-L-α-glutaminato

Se disuelve *terc*-butil *N*-bencil-N^2-({4'-[(3-bromobencil)oxi]bifenil-4-il}carbonil)-L-α-glutaminato (250 mg, 0.38 mmol) en DME (5 mL) bajo nitrógeno en un frasco bomba de 75 mL. Se agregan ácido fenilborónico (51 mg, 0.418 mmol), y $Pd(PPh_3)_4$ (66mg,0.057 mmol) como sólidos antes de la adición de K_2CO_3 (158mg,1.14 mmol) se disuelve en H_2O (1.5 mL). El frasco bomba se sella y la reacción se calienta a reflujo, se agita dos días y se monitorea por TLC. La mezcla de reacción se filtra a través de celita y la celita se enjuaga con MeOH. El disolvente se remueve y el residuo resultante se purifica utilizando HPLC preparativo. El producto se obtiene como un sólido naranja pálido.

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Rendimiento: 154 mg de *terc*-butil *N*-bencil-N^2-{[4'-(bifenil-3-ilmetoxi)bifenil-4-il]carbonil}-L-α-glutaminato en 60% de rendimiento. MS (ESI) *m/z* 655.5; HRMS: calculado para $C_{42}H_{42}N_2O_5$ + H+, 655.31665; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 655.31636.

Etapa D: *N*-bencil-N^2-{[4'-(bifenil-3-ilmetoxi)bifenil-4-il]carbonil}-L-α-glutamina

Se disuelve *terc*-butil *N*-bencil-N^2-{[4'-(bifenil-3-ilmetoxi)bifenil-4-il]carbonil}-L-α-glutaminato (130 mg, 0.199 mmol) en CH_2Cl_2 (3 mL) y se agita en un frasco de 10 mL. Se agrega ácido trifluoroacético (765uL, 10 mmol) y la solución se agita durante 2 horas. El disolvente se remueve y luego se seca bajo vacío. El residuo orgánico se disuelve en un mínimo de acetona y se precipita con hexanos. Rendimiento de 109 mg de *N-bencil*-N^2-{[4'-(bifenil-3-ilmetoxi)bifenil-4-il]carbonil}-L-α-glutamina se obtiene en 91% de rendimiento. MS (ESI) *m/z* 599.4; HRMS: calculado para $C_{38}H_{34}N_2O_5$ + H+, 599.25405; encontrado (ESI-FTMS, $[M+H]^{1+}$), 599.25511.

Ejemplo 15V: *N*-bencil-N^2-({4'-[(3'-metoxibifenil-3-il)metoxi]bifenil-4-il}carbonil)-L-α-glutamina

MS (ESI) *m/z* 627.2; HRMS: calculado para $C_{39}H_{36}N_2O_6$ + H+, 629.26461; encontrado (ESI-FTMS, $[M+H]^{1+}$), 629.26493.

Ejemplo 15W: *N*-bencil-N^2-{[4'-(bifenil-2-ilmetoxi)bifenil-4-il]carbonilI-L-α-glutamina

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MS (ESI) *m/z* 597.3; HRMS: calculado para $C_{38}H_{34}N_2O_5$ + H+, 599.25405; encontrado (ESI-FTMS, $[M-HH]^{1+}$), 599.25523.

Ejemplo 15X: *N*-bencil-N^2-({4'-[(3'-metoxibifenil-2-il)metoxi]bifenil-4-il}carbonil)-L-α-glutamina

MS (ESI) *m/z* 627.3; HRMS: calculado para $C_{39}H_{36}N_2O_6$ + H+, 629.26461; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 629.26484.

Ejemplo 15Y: N^2-({4'-[(3-*terc*-butilfenoxi)metil]bifenil-4-il}carbonil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

Se disuelve tolil-bifenilglutamato (I g, 1.89 mmol) en CCl_4 (20 mL), en un frasco sellado de 40 mL. Se agregan *N*-Bromosuccinimida (NBS) (673 mg, 3.78 mmol) y peróxido de benzoilo (92 mg, 0.378 mmol). La reacción se calienta a 70° C, y se agita durante la noche. La reacción se enfría y el disolvente se remueve. El sólido anaranjado pegajoso restante se purifica mediante cromatografía de columna de sílice utilizando 20% de EtOAc/Hexanos. Se obtiene 400 mg de Bromo-tolil-bifenilglutamato, como un sólido amarillo pálido en 36% de rendimiento.

Se disuelve 3-t-Butilfenol (56 mg, 0.374 mmol) en CH_3CN en un frasco sellado de 20 mL y se agrega K_2CO_3 (258 mg, 1.87 mmol). La reacción se calienta a 80° C y se agita durante 30 minutos. Se agrega el Bromo-tolil-bifenilglutamato (250 mg, 0.41 1 mmol) y la reacción se agita a 80° C durante la noche.

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La reacción se filtra, el disolvente se remueve y el resto de la reacción se purifica mediante cromatografía de columna de sílice para dar el compuesto del título como un sólido blanco se obtiene en 87% de rendimiento. MS (ESI) *m/z* 621.2; MS (ESI) *m/z* 1241.4; HRMS: calculado para $C_{39}H_{44}N_2O_5$ + H+, 621.33230; encontrado (ESI-FTMS, $[M+H]^{1+}$), 621.33234.

Los siguientes compuestos se preparan de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 15 Y:

Ejemplo 15Z: N^2-({4'-[(3,5-di-terc-butilfenoxi)metil]bifenil-4-il}carbonil)-N-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 675.3; MS (ESI) *m/z* 1351.6; HRMS: calculado para $C_{43}H_{52}N_2O_5$ + H+, 677.39490; encontrado (ESI-FTMS, $[M+H]^{1+}$), 677.39504.

Ejemplo 15AA; N-(1,1-dimetil-2-feniletil)-N^2-({4'-[(3-etilfenoxi)metil]bifenil-4-il|carbonil)-L-α-glutamina

MS (ESI) *m/z* 593.2; MS (ESI) *m/z* 1185.4; HRMS: calculado para $C_{37}H_{40}N_2O_5$ + H+, 593.30100; encontrado (ESI-FTMS, $[M+H]^{1+}$), 593.30054.

Ejemplo 15BB: *N*-(1,1-dimetil-2-feniletil)-N^2-({4'-[(3-metoxifenoxi)metil]bifenil-4-il)carbonil)-L-α-glutamina

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MS (ESI) *m/z* 595.3; MS (ESI) *m/z* 1189.6; HRMS: calculado para $C_{36}H_{38}N_2O_6$ + H+, 595.28026; encontrado (ESI-FTMS, $[M+H]^{1+}$), 595.28031.

Ejemplo 16: N^2-[(3'-etoxibifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

El compuesto del título se prepara de acuerdo con procedimientos similares a aquellos descritos en los Ejemplos 7 y 11. MS (ESI) *m/z* 551.2; MS (ESI) *m/z* 1101.4; MS (ESI) *m/z* 573.2; HRMS: calculado para $C_{30}H_{34}N_2O_8$ + H+, 551.23879; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 551.23735.

Los siguientes compuestos se preparan de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 16.

Ejemplo 17A: N^2-[(2'-etoxibifenil-4-il)carbonill-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 551.2; MS (ESI) *m/z* 1101.4; MS (ESI) *m/z* 573.2; HRMS: calculado para $C_{30}H_{34}N_2O_8$ + H+, 551.23879; encontrado (ESI-FTMS, $[M+H]^{1+}$), 551.23739.

Ejemplo 17B: N^2-[(4'-metoxibifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

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MS (ESI) *m/z* 537.2; MS (ESI) *m/z* 1073.4; MS (ESI) *m/z* 559.2; HRMS: calculado para $C_{29}H_{32}N_2O_8$ + H+, 537.22314; encontrado (ESI-FTMS, $[M+H]^{1+}$), 537.22188.

Ejemplo 17C: N^2-[(3'-metoxibifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina

HRMS: calculado para $C_{29}H_{32}N_2O_8$ + H+, 537.22314; encontrado (ESI- FTMS, $[M+H]^{1+}$), 537.22188.

Ejemplo 17D: ácido 4'-{[((1S)-3-carboxi-1-{[(3,4,5-trimetoxibencil)amino]carbonil}propil)amino]carbonil}bifenil-3-carboxílico

MS (ESI) *m/z* 551.1; MS (ESI) *m/z* 1101.3; MS (ESI) *m/z* 573.1; HRMS: calculado para $C_{29}H_{30}N_2O_9$ + H+, 551.20241; encontrado (ESI-FTMS, $[M+H]^{1+}$), 551.2008.

Ejemplo 17E: N^2-[(4'-etilbifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 535.2; MS (ESI) *m/z* 1069.4; HRMS: calculado para $C_{30}H_{34}N_2O_7$ + H+, 535.24388; encontrado (ESI-FTMS, $[M+H]^{1+}$), 535.2425.

Ejemplo 17F: N^2-[(3',4'-dimetoxibifenil-4-il]carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

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MS (ESI) *m/z* 567.2; MS (ESI) *m/z* 1133.5; MS (ESI) *m/z* 589.2; HRMS: calculado para $C_{30}H_{34}N_2O_9$ + H+, 567.23371; encontrado (ESI-FTMS, $[M+H]^{1+}$), 567.23327.

Ejemplo 17G: N^2-[(2',4'-dimetoxibifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 567.2; MS (ESI) *m/z* 1133.5; HRMS: calculado para $C_{30}H_{34}N_2O_9$ + H+, 567.23371; encontrado (ESI-FTMS, $[M+H]^{1+}$), 567.23397.

Ejemplo 17H: N-(3,4,5-trimetoxibencil]-N^2-[(3',4',5'-trimetoxibifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 597.2; MS (ESI) *m/z* 1193.4; HRMS: calculado para $C_{31}H_{36}N_2O_{10}$ + H+, 597.24427; encontrado (ESI-FTMS, $[M+H]^{1+}$), 597.24385.

Ejemplo 17I: N-(1,1-dimetil-2-feniletil)-N^2-[(3'-metoxibifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 489.2; MS (ESI) *m/z* 977.4; MS (ESI) *m/z* 511.2; HRMS: calculado para $C_{29}H_{32}N_2O_5$ + H+, 489.23840; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 489.2373.

Ejemplo 17J: N^2-[(3',4'-dimetoxibifenil-4-il)carbonil]-N-(1,1-dimetil-2-feniletil)-L-α-glutamina

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MS (ESI) *m/z* 519.2; MS (ESI) *m/z* 1037.5; HRMS: calculado para $C_{30}H_{34}N_2O_6$ + H+, 519.24896; encontrado (ESI-FTMS, $[M+H]^{1+}$), 519.248971.

Ejemplo 17K: N-(1,1-dimetil-2-feniletil]-N^2-[(2'-etoxibifenil-4-il)carbonil] -L-α-glutamina

MS (ESI) *m/z* 503.2; MS (ESI) *m/z* 1005.5; HRMS: calculado para $C_{30}H_{34}N_2O_5$ + H+, 503.25405; encontrado (ESI-FTMS, $[M+H]^{1+}$), 503.25421.

Ejemplo 17L: N-(1,1-dimetil-2-feniletil)-N^2-[(3'-fluoro-4'-metilbifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 491.2; MS (ESI) *m/z* 981.5; HRMS: calculado para $C_{29}H_{31}FN_2O_4$ + H+, 491.23406; encontrado (ESI-FTMS, $[M+H]^{1+}$), 491.23402.

Ejemplo 17M: ácido 4-[(4'-Metoxi-3'-metil-bifenil-4-carbonil)-aminol-4-(3,4,5-trimetoxi-bencilcarbamoil)-butírico

MS (ESI) *m/z* 551.2; MS (ESI) *m/z* 1101.5; MS (ESI) *m/z* 1123.5.

Ejemplo 17N: ácido 4-(4-Benzo[1,3]dioxol-5-il-benzoilamino)-4-(3,4,5-trimetoxi-bencilcarbamoil)-butírico

MS (ESI) *m/z* 551.2; MS (ESI) *m/z* 1101.4.

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Ejemplo 17°: N-(1-adamantilmetil)-N^2-[(4'-hidroxibifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 491.4; MS (ESI) *m/z* 981.7; HRMS: calculado para $C_{29}H_{34}N_2O_5$ +H+, 491.25405; encontrado (ESI-FTMS, $[M+H]^{1+}$), 491.25465.

Ejemplo 17P: N^2-[4-(1,3-benzodioxol-5-il)benzoil]-N-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 503.2; MS (ESI) *m/z* 1005.4; MS (ESI) *m/z* 525.2; HRMS: calculado para $C_{29}H_{30}N_2O_6$ + H+, 503.21766; encontrado (ESI-FTMS, $[M+H]^{1+}$), 503.21771.

Ejemplo 17Q: N^2-[(2',4'-dimetoxibifenil-4-ilcarbonil]-N-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 519.2; MS (ESI) *m/z* 1037.5; MS (ESI) *m/z* 541.2; HRMS: calculado para $C_{30}H_{34}N_2O_6$ + H+, 519.24896; encontrado (ESI-FTMS, $[M+H]^{1+}$), 519.24917.

Ejemplo 17R: N^2-[(3'-fluoro-4'-metilbifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 539.3; MS (ESI) *m/z* 1077.6; MS (ESI) *m/z* 561.3; HRMS: calculado para $C_{29}H_{31}FN_2O_7$ + H+, 539.21881; encontrado (ESI-FTMS, $[M+H]^{1+}$), 539.2182.

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Ejemplo 17S: N^2-[(4'-sec-butilbifenil-4-il)carbonil]-N-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 515.4; MS (ESI) *m/z* 1029.9; HRMS: calculado para $C_{32}H_{38}N_2O_4$ + H+, 515.29043; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 515.29203.

Ejemplo 17T: N-(1,1-dimetil-2-feniletil)-N^2-[(4'-isopropilbifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 501.4; MS (ESI) *m/z* 1001.8; HRMS: calculado para $C_{31}H_{36}N_2O_4$ + H+, 501.27478; encontrado (ESI-FTMS, $[M-HH]^{1+}$), 501.27468.

Ejemplo 17U: N-(1,1-dimetil-2-feniletil)-N^2-(1,1':4',1"-terfenil-4-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 535.4; MS (ESI) *m/z* 1069.8; HRMS: calculado para $C_{34}H_{34}N_2O_4$ + H+, 535.25913; encontrado (ESI-FTMS, $[M+H]^{1+}$), 535.26044.

Ejemplo 17V: N^2-[(4'-hidroxibifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 521.3; MS (ESI) *m/z* 1043.7; HRMS: calculado para $C_{28}H_{30}N_2O_8$ + H+, 523.20749; encontrado (ESI-FTMS, $[M+H]^{1+}$), 523.20878.

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Ejemplo 17W: N-(1-adamantilmetil)-N^2-({3-[dimetilamino)carbonil]bifenil-4-il}-L-α-glutamina

MS (ESI) *m/z* 546.4; MS (ESI) *m/z* 1091.9; HRMS: calculado para $C_{32}H_{39}N_3O_5$ + H+, 546.29625; encontrado (ESI-FTMS, $[M+H]^{1+}$), 546.29678.

Ejemplo 17X: N-(1-adamantilmetil)-N^2-[(3',5'-dimetilbifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 503.4; MS (ESI) *m/z* 1005.8; HRMS: calculado para $C_{31}H_{38}N_2O_4$ + H+, 503.29043; encontrado (ESI-FTMS, $[M+H]^{1+}$), 503.29107.

Ejemplo 17Y: N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(3'-metilbifenil-4-il)carbonil] -L-α-glutamina

MS (ESI) *m/z* 491.4; MS (ESI) *m/z* 981.7; MS (ESI) *m/z* 513.3; HRMS: calculado para $C_{29}H_{31}FN_2O_4$ + H+, 491.23406; encontrado (ESI-FTMS, $[M+H]^{1+}$), 491.23228.

Ejemplo 17Z: N^2-[(3'-isopropilbifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 549.4; MS (ESI) *m/z* 1097.9; HRMS: calculado para $C_{31}H_{36}N_2O_7$ + H+, 549.25953; encontrado (ESI-FTMS, $[M+H]^{1+}$), 549.26013.

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Ejemplo 17 AA: N^2-[(4'-isopropilbifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 549.4; MS (ESI) *m/z* 1097.9; HRMS: calculado para $C_{31}H_{36}N_2O_7$ + H+, 549.25953; encontrado (ESI-FTMS, $[M+H]^{1+}$), 549.26066.

Ejemplo 17BB: N-(1-adamantilmetil)-N^2-[4-(1-benzofurano-5-il)benzoil]-L-α-glutamina

MS (ESI) *m/z* 515.4; MS (ESI) *m/z* 1029.9; HRMS: calculado para $C_{31}H_{34}N_2O_5$ + H+, 515.25405; encontrado (ESI-FTMS, $[M+H]^{1+}$), 515.25447.

Ejemplo 17CC: N-(1-adamantilmetil]-N^2-[4-(1H-indol-5-il)benzoil]-L-α-glutamina

MS (ESI) *m/z* 514.4; MS (ESI) *m/z* 1027.7; HRMS: calculado para $C_{31}H_{35}N_3O_4$ + H+, 514.27003; encontrado (ESI-FTMS, $[M+H]^{1+}$), 514.27038.

Ejemplo 17DD: N^2-[(3'-etoxibifenil-4-il)carbonill-N-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 521.4; MS (ESI) *m/z* 1041.7; HRMS: calculado para $C_{30}H_{33}FN_2O_5$ + H+, 521.24463; encontrado (ESI-FTMS, $[M+H]^{1+}$), 521.24248.

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Ejemplo 17EE: N-[2-[4-fluorofenil)-1,1-dimetiletil]-N^2-[(3'-metoxibifenil-4-il)carbonil1-L-α-glutamina

MS (ESI) *m/z* 507.3; MS (ESI) *m/z* 1013.7; HRMS: calculado para $C_{29}H_{31}FN_2O_5$ + H+, 507.22898; encontrado (ESI-FTMS, $[M+H]^{1+}$), 507.22717.

Ejemplo 17FF: *N*-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(3'-isopropilbifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 519.4; MS (ESI) *m/z* 1037.7; HRMS: calculado para $C_{31}H_{35}FN_2O_4$ + H+, 519.26536; encontrado (ESI-FTMS, $[M+H]^{1+}$), 519.26474.

Ejemplo 17GG: N^2-[(3'-fluoro-4'-metilbifenil-4-ilcarbonil]-N-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

MS (ESI) *m/z* 509.3; MS (ESI) *m/z* 1017.7; HRMS: calculado para $C_{29}H_{30}F_2N_2O_4$ + H+, 509.22464; encontrado (ESI-FTMS, $[M+H]^{1+}$), 509.22537.

Ejemplo 17HH: N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(4'-isobutilbifenil-4-il)carbonil] -L-α-glutamina

MS (ESI) *m/z* 533.4; MS (ESI) *m/z* 1065.8; HRMS: calculado para $C_{32}H_{37}FN_2O_4$ + H+, 533.28101; encontrado (ESI-FTMS, $[M+H]^{1+}$), 533.28214.

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Ejemplo 17II: N^2-(1,1':4',1"-terfenil-4-ilcarbonil)-N-(3,4,5-trimetoxibencil]-L-α-glutamina

MS (ESI) *m/z* 581.2; MS (ESI) *m/z* 1163.4; HRMS: calculado para $C_{34}H_{34}N_2O_7$ + H+, 583.24388; encontrado (ESI-FTMS, $[M+H]^{1+}$), 583.24414.

Ejemplo 17JJ: N-bencil-N^2-{[3'-(hidroximetil)bifenil-4-il]carbonil)-L-α-glutamina

MS (ESI) *m/z* 445.1; MS (ESI) *m/z* 891.2.

Ejemplo 17KK: *N*-(3,4,5-trimetoxibencil)-N^2-[(2',4',6'-trimetilbifenil-4-il)carbonil]-L-α-glutamina

HRMS: calculado para $C_{31}H_{36}N_2O_7$ + H+, 549.25953; encontrado (ESI- FTMS, $[M+H]^{1+}$), 549.25817.

Ejemplo 17LL: *N*-(1,1-dimetil-2-feniletil)-N^2-[(4'-hidroxibifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 475.2; MS (ESI) *m/z* 949.4; HRMS: calculado para $C_{28}H_{30}N_2O_5$ +H+, 475.22275; encontrado (ESI-FTMS, $[M+H]^{1+}$), 475.22358.

Ejemplo 17MM: N-(1,1-dimetil-2-feniletil)-N^2-[(3'-etoxibifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 503.2; MS (ESI) *m/z* 1005.3; MS (ESI) *m/z* 525.1; HRMS: calculado para $C_{30}H_{34}N_2O_5$ + H+, 503.25405; encontrado (ESI-FTMS, $[M+H]^{1+}$), 503.25252.

Ejemplo 17NN: N^2-[4-(1,3-benzodioxol-5-il)benzoil]-*N*-(3-metilbencil)-L-α-glutamina

MS (ESI) *m/z* 475.1; MS (ESI) *m/z* 949.2; HRMS: calculado para $C_{27}H_{26}N_2O_6$ +H+, 475.18636; encontrado (ESI-FTMS, $[M+H]^{1+}$), 475.1872.

Ejemplo 17OO: N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(4'-hidroxibifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 493.2; MS (ESI) *m/z* 985.4; HRMS: calculado para $C_{28}H_{29}FN_2O_5$ + H+, 493.21333; encontrado (ESI-FTMS, $[M+H]^{1+}$), 493.21327.

Ejemplo 17PP: N^2-[4-(1,3-benzodioxol-5-il)benzoil]-N-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

(1): MS (ESI) *m/z* 521.1; MS (ESI) *m/z* 1041.3; HRMS: calculado para $C_{29}H_{29}FN_2O_6$ + H+, 521.20824; encontrado (ESI-FTMS, $[M+H]^{1+}$), 521.20872; (2): MS (ESI) *m/z* 521.2; MS (ESI) *m/z* 1041.3.

Ejemplo 17QQ: N-bencil-N^2-{4-[(4-hidroxiciclohexil)etinil]benzoil}-L-α-glutamina

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MS (ESI) *m/z* 463.1; MS (ESI) *m/z* 925.3.

Ejemplo 17RR: N^2-[(3'-hidroxibifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

HRMS: calculado para $C_{28}H_{30}N_2O_8$ + H+, 523.20749; encontrado (ESI- FTMS, $[M+H]^{1+}$), 523.20809.

Ejemplo 17SS: *N*-(1,1-dimetil-2-feniletil]-N^2-{[4'-(hidroximetil)bifenil-4-il]carbonil}-L-α-glutamina

MS (ESI) *m/z* 487.1; MS (ESI) *m/z* 975.2; HRMS: calculado para $C_{29}H_{32}N_2O_5$ +H+, 489.23840; encontrado (ESI-FTMS, $[M+H]^{1+}$), 489.2389.

Ejemplo 17TT: N-(1,1-dimetil-2-feniletil)-N^2-[(4'-metilbifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 473.1; MS (ESI) *m/z* 945.3; HRMS: calculado para $C_{29}H_{32}N_2O_4$ +H+, 473.24348; encontrado (ESI-FTMS, $[M+H]^{1+}$), 473.24409.

Ejemplo 17UU: N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(3'-hidroxibifenil-4-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 493.2; MS (ESI) *m/z* 985.4.

Ejemplo 17VV: N^1-bencil-N^2-(4-piridin-4-ilbenzoil)-L-α-glutamina

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MS (ESI) *m/z* 418.2; HRMS: calculado para $C_{24}H_{23}N_3O_4$ + H+, 418.17613; encontrado (ESI_FT, $[M+H]^{1+}$), 418.17461.

Ejemplo 17WW: N^1-bencil-N^{2-}(1,1'-bifenil-3-ilcarbonil)-L-α-glutamina

MS (ESI) *m/z* 417.1; MS (ESI) *m/z* 833.1; HRMS: calculado para $C_{25}H_{24}N_2O_4$ +H+, 417.18088; encontrado (ESI-FTMS, $[M+H]^{1+}$), 417.18049.

Ejemplo 17XX: N^1-bencil-N^{2-}(3-tien-2-ilbenzoil)-L-α-glutamina

MS (ESI) *m/z* 423.1; MS (ESI) *m/z* 845; HRMS: calculado para $C_{23}H_{22}N_2O_4S$ +H+, 423.13730; encontrado (ESI-FTMS, $[M+H]^{1+}$), 423.1383.

Ejemplo 17YY: N^1-bencil-N^2-[(3-cloro-1,1'-bifenil-4-il)carbonil1-L-α-glutamina

MS (ESI) *m/z* 451.1; MS (ESI) *m/z* 901; HRMS: calculado para $C_{25}H_{23}ClN_2O_4$ + H+, 451.14191; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 451.1417.

Ejemplo 17ZZ: N^1-bencil-N^2-[(3-fluoro-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

HRMS: calculado para $C_{25}H_{23}FN_2O_4$ + H+, 435.17146; encontrado (ESI- FTMS, $[M+H]^{1+}$), 435.17091.

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Ejemplo 17AAA: N^1-bencil-N^2-[(2,6-dimetoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

HRMS: calculado para $C_{27}H_{28}N_2O_6$ + H+, 477.20201; encontrado (ESI- FTMS, $[M+H]^{1+}$), 477.20098.

Ejemplo 17BBB: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metoxi-1,1'-bifenil-3-il)-L-α-glutamina

MS (ESI) *m/z* 509.2; MS (ESI) *m/z* 1017.2; HRMS: calculado para $C_{31}H_{28}N_2O_5$ + H+, 509.20710; encontrado (ESI-FTMS, $[M+H]^{1+}$), 509.20875.

Ejemplo 18: N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-N-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 673.4; MS (ESI) *m/z* 1345.9; HRMS: calculado para $C_{37}H_{40}N_2O_{10}$ + H+, 673.27557; encontrado (ESI-FTMS, $[MH-H]^{1+}$), 673.27498.

Ejemplo 19:

Los siguientes compuestos se preparan de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 18.

Ejemplo 19A: *N*-(1-adamantilmetil)-N^2-({4'-[(3-metoxibencil)oxi]bifenil-4-il}carbonil)-L-α-glutamina

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MS (ESI) *m/z* 611.5; MS (ESI) *m/z* 1222; HRMS: calculado para $C_{37}H_{42}N_2O_6$ +H+, 611.31156; encontrado (ESI-FTMS, $[M+H]^{1+}$)$_5$ 611.31164.

Ejemplo 19B: *N*-(1-adamantilmetil)-N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-1-α-glutamina

MS (ESD *m/z* 641.5; MS (ESI) *m/z* 1282; HRMS: calculado para $C_{38}H_{44}N_2O_7$ +H+, 641.32213; encontrado (ESI-FTMS, $[M+H]^{1+}$), 641.32171.

Ejemplo 19C: N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-N-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 625.5; MS (ESI) *m/z* 1249.9; HRMS: calculado para $C_{37}H_{40}N_2O_7$ + H+, 625.29083; encontrado (ESI-FTMS, $[M+H]^{1+}$), 625.2906.

Ejemplo 19D: *N*^{2}-({4'-[(3,5-dimetilbencil)oxi]bifenil-4-il}carbonil)*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 641.5; MS (ESI) *m/z* 1282.

Ejemplo 19E: *N*^{2}-[(4'-{[3,5-bis(trifluorometil)bencil]oxi}bifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina

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MS (ESD *m/z* 749.5; MS (ESD *m/z* 771.5; HRMS: calculado para $C_{37}H_{34}F_6N_2O_8$ + H+, 749.22921; encontrado (ESI-FTMS, $[M+H]^{1+}$), 749.2297.

Ejemplo 19F: N-(1,1-dimetil-2-feniletil)-N^2-({4'-[(3-metoxibencil)oxi]bifenil-4-il}carbonil)-L-α-glutamina

MS (ESD *m/z* 595.3; MS (ESD *m/z* 1189.5; HRMS: calculado para $C_{36}H_{38}N_2O_6$ + H+, 595.28026; encontrado (ESI-FTMS, $[M+H]^{1+}$), 595.28185.

Ejemplo 19G: N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-N-(6-hidroxihexil)-L-α-glutamina

MS (ESD *m/z* 591.2; HRMS: calculado para $C_{33}H_{40}N_2O_8$ + H+, 593.28574; encontrado (ESI-FTMS, $[M+H]^{1+}$), 593.28726.

Ejemplo 19H: N^2-({4'-[(3-metoxibenil)oxi]bifenil-4-il}carbonil)-N-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI-FTMS) *m/z* 643.26499; MS (ESI-FTMS) *m/z* 643.26501;

HRMS: calculado para $C_{36}H_{38}N_2O_9$ + H+, 643.26501; encontrado (ESI-FTMS, $[M+H]^{1+}$), 643.26499.

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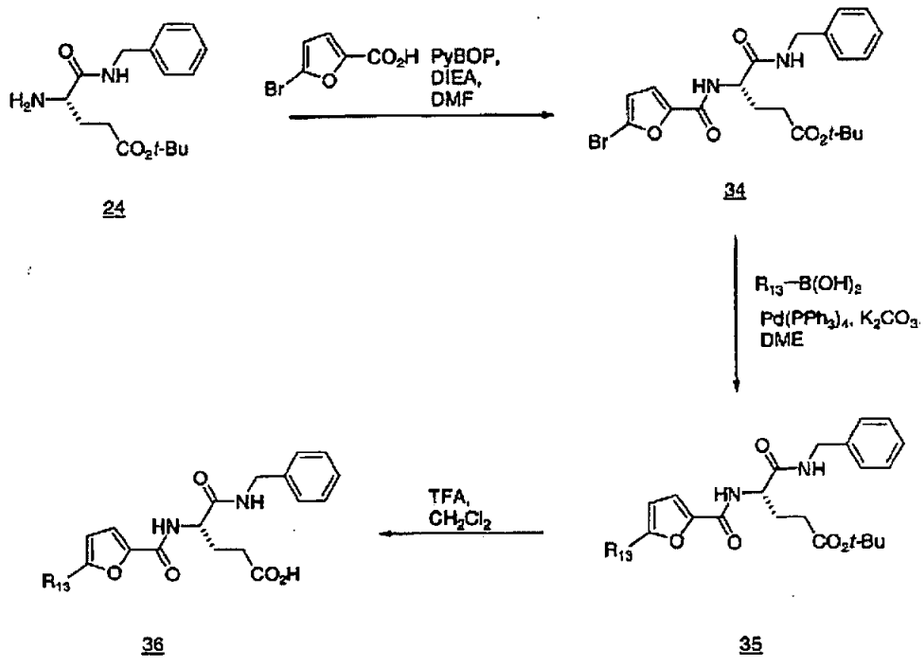
Esquema 11



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Ejemplo 20: N^1-bencil-N^2-(5-fenil-2-furoil)-L-α-glutamina

Etapa A: *terc*-butil N^1-bencil-N^2-(5-bromo-2-furoil)-L-α-glutaminato

Se disuelve *terc*-butil N^1-bencil-L-α-glutaminato (2.33 g, 7.98 mmol) en DMF (7 mL) bajo nitrógeno. Se agrega ácido 5-bromofuróico (1.52 g, 7.98 mmol), seguido por adición de PyBOP (5.00 g, 9.6 mmol). Finalmente, se agrega en forma de gota DIEA (1.67 mL, 9.6 mmol) durante 5 minutos por vía de un embudo de adición. La reacción se monitorea por TLC y se agita durante la noche. La solución se diluye con EtOAc (250 mL), se lava consecutivamente con H_2O, 10% de HCl, $NaHCO_3$ saturado, solución salina, y luego se seca sobre Na_2SO_4. Después el disolvente se evapora, el residuo crudo se disuelve en éter y se lava con LiBr ac. (2 x 250 mL) y se seca sobre Na_2SO_4. Se remueve éter, dejando un aceite que se purifica adicionalmente en una columna de SiO_2 utilizando

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33%-40% de EtOAc/Hex como el disolvente. El producto es el tercer punto de la columna y un sólido naranja pegajoso. Rendimiento 1.60 g de *terc*-butil *N*^{1}-*bencil*-*N* -(5-bromo-2-furoil)-L-α-glutaminato en 43% de rendimiento.

Etapa B: *terc*-butil *N*^{1}-bencil-*N*^{2}-(5-fenil-2-furoil)-L-α-glutaminato

HRMS: calculado para $C_{27}H_{30}N_2O_5$ + Na+, 485.20469; encontrado (ESI_FTMS, $[M+Na]^{1+}$), 485.20466.

Etapa C: *N*^{1}-bencil-*N*^{2}-(5-fenil-2-furoil)-L-α-glutamina

HRMS: calculado para $C_{23}H_{22}N_2O_5$ + H+, 407.16015; encontrado (ESI_FTMS, $[M+H]^{1+}$), 407.15841.

Ejemplo 21:

Los siguientes compuestos se preparan de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 20.

Ejemplo 21A: *N*^{1}-bencil-*N*^{2}-[5-(3-etoxifenil)-2-furoil]-L-α-glutamina

Etapa B: *terc*-butil *N*^{1}-bencil-*N*^{2}-[5-3-etoxifenil)-2-furoil]-L-α-glutaminato

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HRMS: calculado para $C_{29}H_{34}N_2O_6$ + H+, 507.24896; encontrado (ESI_FTMS, $[M+H]^{1+}$), 507.24894.

Etapa C: N^1-bencil-N^2-[5-(3-etoxifenil)-2-furoil]-L-α-glutamina

HRMS: calculado para $C_{25}H_{26}N_2O_6$ + H+, 451.18636; encontrado (ESI_FTMS, $[M+H]^{1+}$), 451.18545.

Ejemplo 21B: N^1-bencil-N^2-[5-(3,5-dimetilfenil)-2-furoil]-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-[5-(3,5-dimetilfenil)-2-furoil]-L-α-glutaminato

HRMS: calculado para $C_{29}H_{34}N_2O_5$ + H+, 491.25405; encontrado (ESI_FTMS, $[M+H]^{1+}$), 491.2538.

Etapa C: N^1-bencil-N^2-[5-(3,5-dimetilfenil)-2-furoil]-L-α-glutamina

HRMS: calculado para $C_{25}H_{26}N_2O_5$ + H+, 435.19145; encontrado (ESI_FTMS, $[M+H]^{1+}$), 435.19034.

Ejemplo 21C: N^1-bencil-N^2-(2,2'-bifurano-5-ilcarbonil)-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-(2,2'-bifurano-5-ilcarbonil)-L-α-glutaminato

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HRMS: calculado para $C_{25}H_{28}N_2O_6$ + H+, 453.20201; encontrado (ESI_FTMS, $[M+H]^{1+}$), 453.20173.

Etapa C: N^1-bencil-N^2-(2,2'-bifurano-5-ilcarbonil)-L-α-glutamina

HRMS: calculado para $C_{21}H_2ON_2O_6$ + H+, 397.13941; encontrado (ESI_FTMS, $[M+H]^{1+}$), 397.13777.

Ejemplo 21D: N^1-bencil-N^2-(5-tien-il-2-furoil)-L-α-glutamina

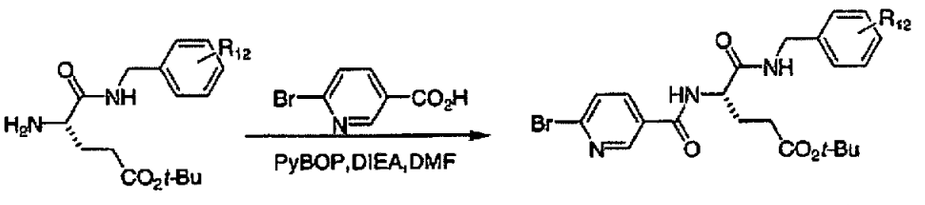
Etapa B: *terc*-butil N^1-bencil-N^2-(5-tien-2-il-2-furoil)-L-α-glutaminato

HRMS: calculado para $C_{25}H_{28}N_2O_5S$ + H+, 469.17917; encontrado (ESI_FTMS, $[MH-H]^{1+}$), 469.1789.

Etapa C: N^1-bencil-N^2-(5-tien-2-il-2-furoil)-L-α-glutamina

HRMS: calculado para $C_{21}H_2ON_2O_5S$ + H+, 413.11657; encontrado (ESI_FTMS, $[M+H]^{1+}$), 413.11511.

Esquema 12



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Ejemplo 22:

Los siguientes compuestos se preparan de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 20.

Ejemplo 22A; N^1-bencil-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina

Etapa A: *terc*-butil N^1-bencil-N^2-[(6-bromopiridin-3-il)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 476.1; MS (ESI) *m/z* 951.1; HRMS: calculado para $C_{22}H_{26}BrN_3O_4$ + H+, 476.11794; encontrado (ESI-FTMS, $[M+H]^{1+}$), 476.11935.

Etapa B: *terc*-butil N^1-bencil-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 474.2; HRMS: calculado para $C_{28}H_{31}N_3O_4$ + H+, 474.23873; encontrado (ESI- FTMS, $[M+H]^{1+}$), 474.23861.

Etapa C: N^1-bencil-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 418.1; HRMS: calculado para $C_{24}H_{23}N_3O_4$ + H+, 418.17613; encontrado (ESI- FTMS, $[M+H]^{1+}$), 418.17674.

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Ejemplo 22B: N^1-(3-metoxibencil)-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina

Etapa A: *terc*-butil N^2-[(6-bromopiridin-3-il)carbonil]-N^1-(3-metoxibencil)-L-α-glutaminato

MS (ESI) *m/z* 506.1; MS (ESI) *m/z* 1011.1; HRMS: calculado para $C_{23}H_{28}BrN_3O_5$ + H+, 506.12851; encontrado (ESI-FTMS, $[M+H]^{1+}$), 506.12839.

Etapa B: *terc*-butil N^1-(3-metoxibencil)-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutaminato

MS (ESI) *m/z* 504.2; HRMS: calculado para $C_{29}H_{33}N_3O_5$ + H+, 504.24930; encontrado (ESI- FTMS, $[M+H]^{1+}$), 504.24835.

Etapa C: N^1-(3-metoxibencil)-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina

MS (ESI) *m/z* 448.1; HRMS: calculado para $C_{25}H_{25}N_3O_5$ + H+, 448.18670; encontrado (ESI- FTMS, $[M+H]^{1+}$), 448.18686.

Ejemplo 22C: N^2-[(2,2'-dimetil-1,1'-bifenil-4-il]carbonil]-N^1-(3-metoxibencil)-L-α-glutamina

Etapa B: *terc*-butil N^2-[(2,2'-dimetil-1,1'-bifenil-4-il)carbonil]-N^1-(3-metoxibencil)-L-α-glutaminato

606

MS (ESI) *m/z* 531.3; MS (ESI) *m/z* 1061.4; HRMS: calculado para $C_{32}H_{38}N_2O_5$ + H+, 531.28535; encontrado (ESI_FTMS, $[M+H]^{1+}$), 531.2855.

Etapa C: N^2-[(2,2'-dimetil-1,1'-bifenil-4-il)carbonil]-N^1-(3-metoxibencil)-L-α-glutamina

HRMS: calculado para $C_{28}H_{30}N_2O_5$ + H+, 475.22275; encontrado (ESI_FTMS, $[MH-H]^{1+}$), 475.22271.

Ejemplo 22D: N^2-(4-bromobenzoil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

MS (ESI) *m/z* 507; MS (ESI) *m/z* 1015.1; HRMS: calculado para $C_{22}H_{25}BrN_2O_7$ + H+, 509.09179; encontrado (ESI-FTMS, $[M+H]^{1+}$), 509.09078.

Ejemplo 22E: N^2-(4-bromobenzoil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

MS (ESI) *m/z* 461.1; MS (ESI) *m/z* 921.2; HRMS: calculado para $C_{22}H_{25}BrN_2O_4$ + H+, 461.10705; encontrado (ESI-FTMS, $[M+H]^{1+}$), 461.10805.

Ejemplo 22F: N-(1-adamantilmetil)-N^2-(4-bromobenzoil)-L-α-glutamina

607

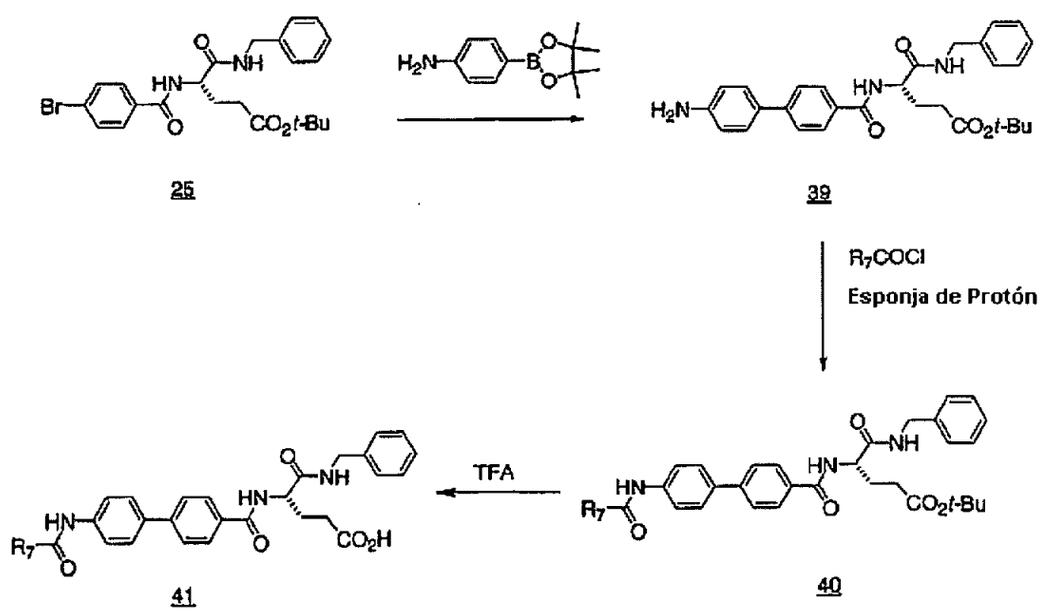
MS (ESI) *m/z* 477.3; MS (ESI) *m/z* 953.5; HRMS: calculado para $C_{23}H_{29}BrN_2O_4$ + H+, 477.13835; encontrado (ESI-FTMS, $[M+H]^{1+}$), 477.13801.

Ejemplo 22G: N^2-(4-bromobenzoil)-*N*-(3-metilbencil)-L-α-glutamina

MS (ESI-FTMS) *m/z* 433.07562; MS (ESI-FTMS) *m/z* 433.07575;

HRMS: calculado para $C_{20}H_{21}BrN_2O_4$ + H+, 433.07575; encontrado (ESI-FTMS, $[M+H]^{1+}$), 433.07562.

Esquema 13



Ejemplo 23: N^2-{[4'-(acetilamino)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutamina

601

Etapa A: *terc*-butil N^2-[(4'-amino-1,1'-bifenil-4-il)carbonil]-N^1-bencil-L-α-glutaminato

Se disuelve terc-butil éster de ácido 4-Bencilcarbamoil-4-(4-bromo-benzoilamino)-butírico (3.0 g, 6.31 mmol, 1 equiv.) en DME (60 mL) se agrega a 4-(4,4,5,5,)-tetrametil-1,3,2-dioxoborolan-2-il)anilina (1.38 g, 6.31 mmol, 1 equiv.) y $Pd(PPh_3)_4$ (728 mg, 0.063 mmol, 0.1 equiv.). La mezcla se agita durante 30 minutos antes de la adición de K_2CO_3 ac. (1.74 g, 12.6 mmol, 2 equiv.) en 12 mL de H_2O. La mezcla se tapa en un recipiente sellado y se agita durante la noche a 80° C. La reacción se completa como se determina mediante TLC. La mezcla se filtra sobre celita, el disolvente se remueve, y el sólido tostado resultante se diluye con EtOAc (200 mL) y se lava consecutivamente con H_2O, 10% de HCl, y solución salina, y luego se seca sobre Na_2SO_4. El sólido se purifica mediante cromatografía de columna (gel de sílice, 41% de Acetona/Hexanos) para dar 1.89 g de *terc*-butil N^2-[(4'-amino-1,1'-bifenil-4-il)carbonil]-N^1-bencil-L-α-glutaminato en 61% de rendimiento. MS (ESI) *m/z* 488.2; HRMS: calculado para $C_{29}H_{33}N_3O_4$ + H+, 488.25438; encontrado (ESI_FTMS, $[M+H]^{1+}$), 488.25433.

Etapa B: isopropil N^2-{[4'-(acetilamino)-1,1'-bifenil-4-il]carbonil}-N^1-*bencil*-L-α-glutaminato

terc-butil éster de ácido 4-[(4'- Amino-bifenil-4-carbonil)-amino]-4-bencilcarbamoil-butírico (300 mg, 0.62 mmol, 1 equiv.) se disuelve en CH_2Cl_2 (20 mL) y se enfría a 0°C

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seguido por la adición de esponja de protón (266 mg, 1.24 mmol, 2 equiv.). La mezcla se agita 30 minutos antes de la adición de cloruro de acetilo (48 μL, 0.68 mmol, 1.1 equiv.) La mezcla se agita a 0° C durante 1.5 hrs y se le permite calentar a temperatura ambiente. La reacción se completa como se determina mediante TLC. La mezcla se lava consecutivamente con H_2O, $NaHCO_3$ satur., y solución salina, y luego se seca sobre Na_2SO_4. El sólido tostado se purifica mediante HPLC preparativo para dar 85 mg de isopropil N^2-{[4'-(acetilamino)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutaminato en 26% de rendimiento. MS (ESI) *m/z* 557.2; MS (ESI) *m/z* 279.1.

Etapa C: N^2-{[4'-(acetilamino)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutamina

Se disuelve *terc*-butil éster de ácido 4-[(4'-Acetilamino-bifenil-4-carbonil)-amino]-4-bencilcarbamoil-butírico (75 mg) en dicloroetano (4 mL) y se agrega ao TFA (2 mL). La mezcla se agita a temperatura ambiente durante 3 hrs. La reacción se completa como se determina mediante TLC. El disolvente se remueve y el sólido resultante se purifica mediante HPLC preparativo para dar N^2-{[4'-(acetilamino)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutamina in 54% de rendimiento (37 mg).

MS (ESI) *m/z* 474.2; MS (ESI) *m/z* 947.3; HRMS: calculado para $C_{27}H_{27}N_3O_5$ + H+, 474.20235; encontrado (ESI_FTMS, $[M+H]^{1+}$), 474.20274.

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Ejemplo 24:

Los siguientes compuestos se preparan de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 23.

Ejemplo 24A: N^1-bencil-N^2-{[4'-(2-furoilamino)-1,1'-bifenil-4-il1carbonil}-L-α-glutamina

Etapa B: *terc*-butil N^1-bencil-N^2-{[4'-(2-furoilamino)-1,1'-bifenil-4-il]carbonil}-L-α-glutaminato

MS (ESI) *m/z* 582.3; MS (ESI) *m/z* 1163.5; HRMS: calculado para $C_{34}H_{35}N_3O_6$ + H+, 582.25986; encontrado (ESI_FTMS, $[MH-H]^{1+}$), 582.26058.

Etapa C: N^1-bencil-N^2-{[4'-(2-furoilamino)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina

MS (ESI) *m/z* 526.2; MS (ESI) *m/z* 1051.3; HRMS: calculado para $C_{30}H_{27}N_3O_6$ + H+, 526.19726; encontrado (ESI_FTMS, $[M+H]^{1+}$), 526.19773.

Ejemplo 24B: N^1-bencil-N^2-({4'-[(4-fluorobenzoil)amino]-1,1'-bifenil-4-il)carbonil)-L-α-glutamina

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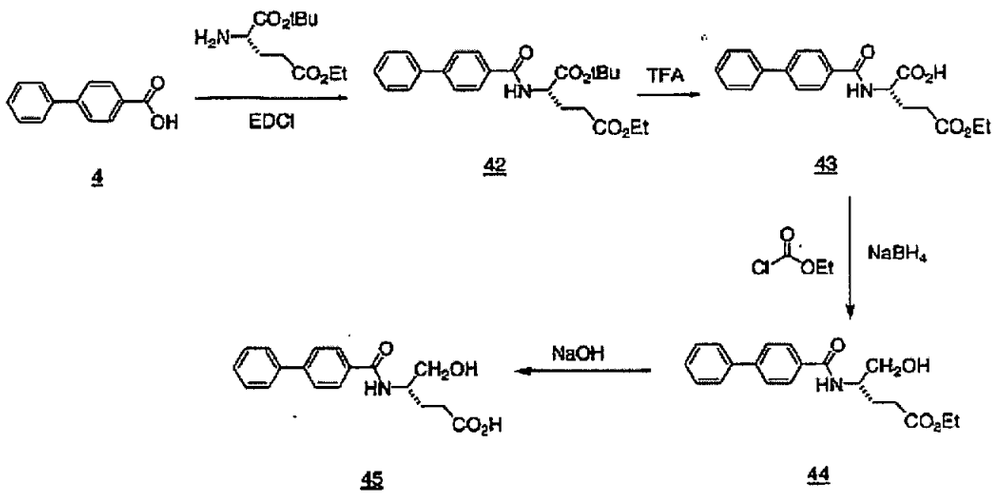
Etapa B: *terc*-butil N^1-bencil-N^2-({4'-[(4-fluorobenzoil)amino]-1,1'-bifenil-4-il}carbonil)-L-α-glutaminato

Etapa C: N^1-bencil-N^2-({4'-[(4-fluorobenzoil)amino]-1,1'-bifenil-4-il}carbonil)-L-α-glutamina

Ejemplo 24C: N^2-{[4'-(benzoilamino)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutamina

HRMS: calculado para $C_{32}H_{29}N_3O_5$ - H+, 534.20345; encontrado (ESI_FTMS, $[M-H]^1$-), 534.2024.

Esquema 14



Ejemplo 25: ácido 4-[(Bifenil-4-carbonil)-amino]-5-hidroxi-pentanóico

Etapa A: éster de 1-*terc*-butilo 5-metil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanodióico

612

Se disuelven ácido 4-Difenil carboxílico (3.57 g, 18 mmol) y EDCI (4.28 g, 22.3 mmol, 1.2 equiv.) en DMF (40 mL). La mezcla se agita a temperatura ambiente durante 0.5 hrs. Se agrega H-Glu(OMe)OtBu (5.02 g, 19.8 mmol, 1.1 equiv.), seguido por la adición de Et_3N (6.77 mL, 48.6 mmol, 2.7 equiv.) y DMAP (330 mg, 2.7 mmol, 15%). La mezcla se agita durante la noche bajo N_2. La mezcla de reacción luego se diluye con EtOAc y se lava con H_2O y solución salina. La capa orgánica se seca sobre $MgSO_4$, se concentra, y se purifica mediante cromatografía de columna (20% de EtOAc/Hexano) para producir 3.2 g de 1-terc-butil éster 5-metil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanodióico en 44.7% de rendimiento. MS (ESI) *m/z* 396.

Etapa B: 5-metil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanodióico

Se disuelve 1-terc-butil éster 5-metil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanodióico (1.5 g, 3.8 mmol) en dicloroetano (26 mL) y la mezcla se agrega a TFA (13 mL). La mezcla se agita a temperatura ambiente durante 4 hrs. El TLC indica que la reacción se completa. El disolvente se evapora mediante rotavapor. El sólido obtenido se lava con EtOAc y agua. Después de secar, 5-metil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanodióico se obtiene en 87% de rendimiento (1.128 g). MS (ESI) *m/z* 342.

Etapa C: metil éster de ácido 4-[(Bifenil-4-carbonil)-amino]-5-hidroxi-pentanóico

Se disuelve 5-metil éster de ácido 2-[(Bifenil-4-carbonil)-amino]-pentanodióico (1.128 g, 3.30 mmol, 1.0 equiv.) en THF (35 mL). La mezcla se enfría a -20° C, seguido por la adición de Et_3N (343 mg, 3.3 mmol, 1.0 equiv.) y cloroformato de etilo (358 mg, 3.3 mmol, 1.0 equiv.). Después de agitar durante 20 minutos, se agrega $NaBH_4$ (375 mg, 9.9 mmol, 3 equiv.) y la temperatura se eleva a -10° C. Después de agitar durante 5 min, se introduce MeOH (3O mL) y la mezcla se agita adicionalmente durante 20 min a esta temperatura y luego a 0° C durante 20 min. Luego se agrega lentamente HCl 1N para apagar la reacción. El disolvente se evapora y el residuo se particiona entre EtOAc y H_2O. La capa orgánica se lava con solución salina, se seca sobre $MgSO_4$, y se remueve el disolvente mediante rotavapor. La mezcla cruda luego se purifica mediante cromatografía de columna (gel de sílice, 3% de $MeOH/CH_2Cl_2$) para producir 333 mg de metil éster de ácido 4-[(Bifenil-4-carbonil)-amino]-5-hidroxi-pentanóico en 31 % de rendimiento. MS (ESI) *m/z* 328.

Etapa D: ácido 4-[(Bifenil-4-carbonil)-amino]-5-hidroxi-pentanóico

Una solución de metil éster de ácido 4-[(Bifenil-4-carbonil)-amino]-5-hidroxi-pentanóico (333 mg, 1.06 mmol) en THF (10 mL) y MeOH (1.27 mL) se agrega a NaOH 1N (1.27 mL, 1.27 mmol, 1.2 equiv) a temperatura ambiente. La mezcla se agita

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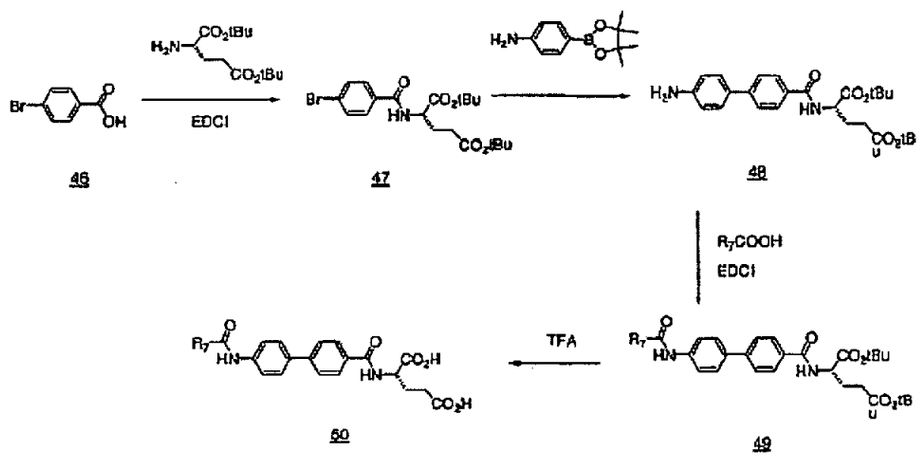
durante 2 horas y El TLC indica que la reacción se completa. El disolvente se remueve y el residuo se disuelve en agua. Después de ajustar el pH a 4 con HCl 1N, el sólido se precipita de la solución. El sólido luego se recolecta mediante filtración, se lava con agua, y se seca bajo vacío durante la noche para producir 240 mg de ácido 4-[(Bifenil-4-carbonil)- amino]-5-hidroxi-pentanóico en 76.7% de rendimiento. MS (ESI) *m/z* 314.

Esquema 15



Ejemplo 26: ácido *N*-({4'-[(fenilacetil)amino]-1,1'-bifenil-4-il}carbonil)-1-glutámico

Etapa A: di-terc-butil éster de ácido 2-(4-Bromo-benzoilamino)-pentanodióico

Una solución de ácido 4-Bromobenzoico (4 g, 19.9 mmol, 1 equiv) en DMF (140 mL) se agrega a EDCI (5.72 g, 29.8 mmol, 1.5 equiv.) y la mezcla se agita a temperatura ambiente durante 25 min. Luego se agrega Et_3N (6.9 mL, 49.7 mmol, 2.5 equiv), seguido por adición de DMAP (486 mg, 4.0 mmol, 20%). La mezcla de reacción se le permite agitar a temperatura

ambiente durante la noche. La reacción se completa como se determina mediante TLC. El DMF se remueve mediante "rotavap" y el residuo se particiona entre EtOAc y solución salina. La capa orgánica se separa, se seca sobre $MgSO_4$ y se concentra. La mezcla cruda se purifica mediante cromatografía de columna (gel de sílice, 20% de EtOAc/Hexano) para dar 4.2 g de di-terc-butil éster de ácido 2-(4-Bromo-benzoilamino)-pentanodióico en 47.7% de rendimiento. MS (ESI) *m/z* 441.

Etapa B: di- terc-butil éster de ácido 2-[(4'-Amino-bifenil-4-carbonil)-amino]-pentanodióico

Se disuelven 4-(4,4,5,5-Tetrametil-[1,3,2]dioxaborolan-2-il)-fenilamina (1.34 g, 6.104 mmol, 1 equiv.) y ácido de di-terc-butil éster 2-(4-Bromo-benzoilamino)-pentanodióico (2.7 g, 6.104 mmol, 1 equiv.) en DME (120 mL). Una solución de K_4CO_3 (1.68 g, 12.21 mmol, 2 equiv.) en 30 mL de agua se inyecta en la mezcla, seguido por la adición de $Pd(PPh_3)_4$ (352 mg, 0.31 mmol, 5%). La mezcla se calienta a reflujo durante la noche. La reacción se completa como se determina mediante TLC. Trabajo regular y cromatografía de columna (gel de sílice, 30-40% de EtOAc/n-Hexano) produce 2.3 g de di-terc-butil éster de ácido 2-[(4'-Amino-bifenil-4-carbonil)-amino]-pentanodióico en 83 % de rendimiento. MS (ESI) *m/z* 453.

Etapa C: di-terc-butil éster de ácido Fenilacetilamino-bifenil-4-carbonil)-amino]-pentanodióico

616

Una solución de ácido fenilacético (89 mg, 0.65 mmol, 1 equiv) en DMF (10 mL) se agrega a EDCI (188 mg, 0.98 mmol, 1.5 equiv.). Después de agitar durante 20 min, se agrega di-terc-butil éster de ácido 2-[(4'-Amino-bifenil-4-carbonil)-amino]-pentanodióico (297 mg, 0.65 mmol, 1 equiv.), seguido por la adición de Et_3N (0.23 mL, 1.64 mmol, 2.5 equiv.) y DMAP (16 mg, 0.13 mmol, 20%). La mezcla de reacción se le permite agitar a temperatura ambiente durante la noche. La reacción se completa como se determina mediante TLC. El DMF se remueve y el residuo se disuelve en EtOAc. La capa orgánica se lava con H_2O y solución salina, y luego se seca sobre $MgSO_4$. Después el disolvente se evapora, el residuo crudo se purifica por HPLC para dar 45 mg de di-terc-butil éster de ácido 2-[(4'-fenilacetilamino-bifenil-4-carbonil)-amino]-pentanodióico en 12 % de rendimiento. MS (ESI) *m/z* 573.

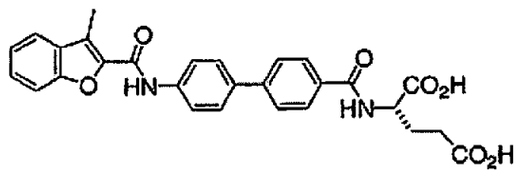
Etapa D: ácido N-({4'-[(fenilacetil)amino]-1,1'-bifenil-4-il}carbonil)-1-glutámico

Se disuelve di-terc-butil éster de ácido 2-[(4'-fenilacetilamino-bifenil-4-carbonil)-amino]-pentanodioico (45 mg) en dicloroetano (3 mL) y se agrega a TFA (1 mL). La mezcla se agita a temperatura ambiente durante 3 hrs. La reacción se completa como se determina mediante TLC. El disolvente se remueve y el sólido resultante se seca bajo vacío durante la noche. Se obtiene ácido N-({4'[(fenilacetil)amino]-1,1'-bifenil-4-il}carbonil)-1-

617

glutámico en 84.2% de rendimiento (30.3 mg). MS (ESI) *m/z* 461.

Ejemplo 27: ácido N-[(4'-{[(3-Metil-1-benzofurano-2-il)carbonil]-amino)-1,1'-bifenil-4-il)carbonil]-1-glutámico



El compuesto del título se prepara de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 26.

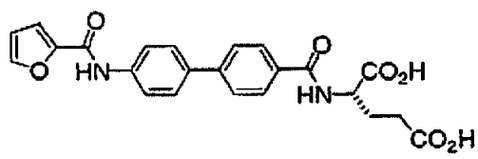
Etapa C: di-terc-butil éster de ácido 2-({4'-[(3-Metil-benzofurano-2-carbonil)-amino]-bifenil-4- carbonil}-amino)-pentanodióico

El acoplamiento EDCI entre ácido 3-Metilbenzofurano 2 carboxílico (139 mg, 0.79 mmol) y di-terc-butil éster de ácido 2-[(4'-Amino-bifenil-4-carbonil)-amino]-pentanodióico (358 mg, 0.79 mmol, 1 equiv.) se lleva a cabo de acuerdo con el procedimiento en la etapa C del Ejemplo 5 para dar di-terc-butil éster de ácido 2-({4'-[(3-Metil-benzofurano-2-carbonil)-amino]-bifenil-4-carbonil}-amino)- pentanodióico en 12.4% de rendimiento (60 mg). MS (ESI) *m/z* 611.

Etapa D: ácido N-[(4'-{[(3-Metil-1-benzofurano-2-il)carbonil]-amino}-1,1'-bifenil-4-il)carbonil]-1-glutámico

La hidrólisis de di-terc-butil éster de ácido 2-({4'-[(3-Metil-benzof uran-2-carbonil)-amino]-bifenil-4-carbonil}-amino)-pentanodióico (60 mg) se lleva a cabo de acuerdo con el procedimiento en la etapa D del Ejemplo 5 para dar ácido *N*-[(4'-{[(3-Metil-1-benzofurano-2-il)carbonil]-amino}-1,1'-bifenil-4-il)carbonil]-1-glutámico en 59 % de rendimiento (28.9 mg). MS (ESI) *m/z* 499.

Ejemplo 28: ácido *N*-{[4'-(2-furoilamino)-1,1'-bifenil-4-illcarbonil}-1-glutámico



Etapa A: di-terc-butil éster de ácido 2-({4'-[(Furano-2-carbonil)-amino]-bifenil-4-carbonil}-amino)-pentanodióico

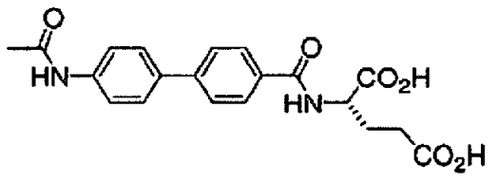
A una solución de di-*terc*-butil éster de ácido 2-[(4'-Amino-bifenil-4-carbonil)-amino]-pentanodióico (350 mg, 0.77 mmol) y ácido 2-furóico (87 mg, 0.77 mmol, 1 equiv.) en DMF (6 mL) se agrega reactivo BOP (409 mg, 0.92 mmol, 1.2 equiv.) y base Hunig (0.16 mL, 0.92 mmol, 1.2 equiv.) bajo N_2. La mezcla se agita a temperatura ambiente durante la noche. La reacción se completa como se determina mediante LC-MS. La mezcla de reacción luego se vierte en agua fría. El sólido precipitado a partir de la mezcla se recolecta mediante filtración. El sólido luego se disuelve en EtOAc, se lava con HCl 1N, $NaHCO_3$ saturado, y solución salina, y luego se seca sobre $MgSO_4$. Después de remover el disolvente, el

sólido se seca bajo vacío durante la noche para proporcionar di-terc-butil éster de ácido 2-({4'-[(Furano-2-carbonil)-amino]-bifenil-4-carbonil}-amino)-pentanodióico en 87 % de rendimiento (369 mg). MS (ESI) *m/z* 549.

Etapa B: ácido *N*-{[4'-(2-furoilamino)-1,1'-bifenil-4-il]carbonil}-1-glutámico

Se disuelve di- terc-butil éster de ácido 2-({4'-[(Furano-2-carbonil)-amino]-bifenil-4-carbonil}-amino)-pentanodióico (369 mg, 0.67 mmol) en dicloroetano (10 mL) y se agrega a TFA (5 mL) a 0° C. El baño frío se remueve después que la adición se completa. La mezcla se agita a temperatura ambiente durante 3 hrs. y la reacción se completa como se determina mediante TLC. Después de remover el disolvente, el residuo se lava 3 veces con EtOAc. El sólido luego se seca bajo vacío para dar ácido 2-({4'-[(Furano-2-carbonil)-amino]-bifenil-4-carbonil}-amino)-pentanodióico en 85.6% de rendimiento (251 mg). MS (ESI) *m/z* 437.

Ejemplo 29: ácido N-{[4'-(acetilamino)-1,1'-bifenil-4-il]carbonil}-1-glutámico



El compuesto del título se prepara de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 28.

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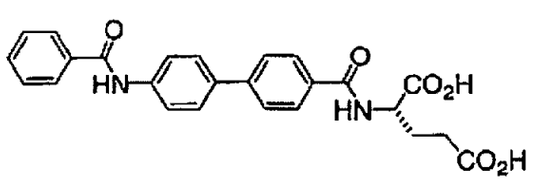
Etapa A: di-terc-butil éster de ácido 2-[(4'-Acetilamino-bifenil-4-carbonil)-amino]-pentanodióico

El acoplamiento BOP de di-*terc*- butil éster de ácido 2-[(4'-Amino-bifenil-4-carbonil)-amino]-pentanodióico (350 mg, 0.77 mmol) se lleva a cabo de acuerdo con los procedimientos en la etapa A del Ejemplo 6B para dar 344 mg de di-terc-butil éster de ácido 2-[(4'-Acetilamino-bifenil-4-carbonil)-amino]-pentanodióico en 89% de rendimiento. MS (ESI) *m/z* 497.

Etapa B: ácido N-{[4'-(acetilamino)-1,1'-bifenil-4-il]carbonil}-1-glutámico

La hidrólisis de di-*terc*- butil éster de ácido 2-[(4'-Acetilamino-bifenil-4-carbonil)-amino]-pentanodióico (344 mg, 0.69 mmol) se lleva a cabo de acuerdo con los procedimientos en la etapa B del Ejemplo 6B para dar 212 mg de ácido 2-[(4'-Acetilamino-bifenil-4-carbonil)-amino]-pentanodióico en 79.7% de rendimiento. MS (ESI) *m/z* 383.

Ejemplo 30: *N*-{[4'-(benzoilamino)-1,1'-bifenil-4-il]carbonil}-L-glutámico



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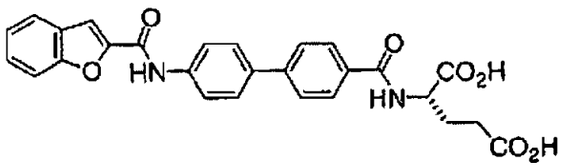
El compuesto del título se prepara de acuerdo con procedimientos similares a aquellos descritos para el Ejemplo 6B.

Etapa D: Ácido N-{[4'-(benzoilamino)-1,1'-bifenil-4-il]carbonil}-1-glutámico

La hidrólisis de di-terc-butil éster de ácido 2-[(4'-Benzoilamino-bifenil-4-carbonil)-amino]-pentanodióico (191 mg) se lleva a cabo de acuerdo con los procedimientos en la etapa D del Ejemplo 6B para dar ácido N-{[4'-(benzoilamino)-1,1'-bifenil-4-il]carbonil}-1-glutámico en 61.6% de rendimiento (93.7 mg). MS (ESI) *m/z* 445.

Ejemplo 31: ácido N-({4'-[(1-benzofurano-2-ilcarbonil)amino]-1,1'-bifenil-4-il}carbonil)-L-glutámico



El compuesto del título se prepara de acuerdo con los procedimientos similares a aquel descrito por el Ejemplo 28.

Etapa A: di-terc-butil éster de ácido 2-({4'-[(Benzofurano-2-carbonil)-amino]-bifenil-4-carbonil}-amino)-pentanodióio

El acoplamiento BOP de di-*terc*- butil éster de ácido 2-[(4'-Amino-bifenil-4-carbonil)-amino]-pentanodióico (349 mg, 0.77

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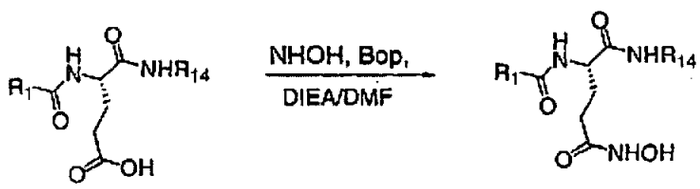
mmol) con ácido 2-Benzofurano carboxílico (124 mg, 0.77 mmol, 1 equiv.) se lleva a cabo de acuerdo con los procedimientos en la etapa A del Ejemplo 6B para dar 185 mg de di-terc-butil éster de ácido 2-({4'-[(Benzofurano-2-carbonil)-amino]-bifenil-4-carbonil}-amino)-pentanodióico en 40% de rendimiento. MS (ESI) *m/z* 597.

Etapa B: ácido N-({4'-[(1-benzofurano-2-ilcarbonil)amino]-1,1'-bifenil-4-il}carbonil)-1-glutámico

La hidrólisis de di-terc-butil éster de ácido 2-({4'-[(Benzofurano-2-carbonil)-amino]-bifenil-4-carbonil}-amino)-pentanodióico (185 mg, 0.31 mmol) se lleva a cabo de acuerdo con los procedimientos en la etapa B del Ejemplo 6B para dar ácido N-({4'-[(1-benzofurano-2-ilcarbonil)amino]-1,1'-bifenil-4-il}carbonil)-1-glutámico en 82.5 % de rendimiento (124 mg). MS (ESI) *m/z* 485.

Esquema 16



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Ejemplo 32: N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]- N^5-hidroxi-L-glutamamida

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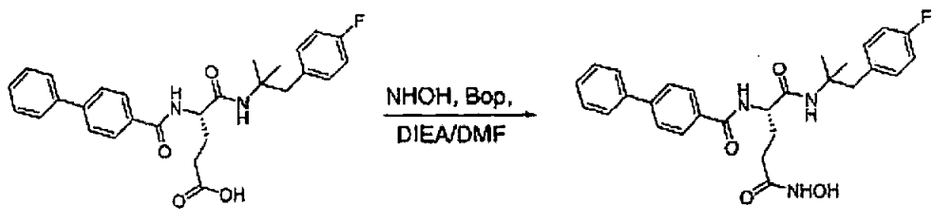

A una solución del ácido carboxílico de partida (0.476 g, 1 mmol) en DMF (4 mL) bajo nitrógeno se agrega reactivo BOP (0.442 g, 1 mmol), seguido por adición de clorhidrato de hidroxilamina (0.076 g, 1.1 mmol), y DIEA (0.38 mL, 2.2 mmol). La mezcla de reacción se agita durante 24 hrs a temperatura ambiente. La mezcla luego se agrega lentamente a 50 mL de agua. El sólido blanco resultante se recolecta, se lava varias veces con agua y se seca bajo vacío para dar 350 mg de N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-N^5-hidroxi-L-glutamamida.

Ejemplo 33:

Los siguientes compuestos se preparan de acuerdo con procedimientos similares a aquellos descritos en el Ejemplo 32.

Ejemplo 33A: N^2-(1,1'-bifenil-4-ilcarbonil)-N^5-hidroxi-N^1-(3,4,5-trimetoxibencil)-L-glutamamida

MS (ESI) *m/z* 522.2; HRMS: calculado para $C_{28}H_{31}N_3O_7$ + H+, 522.22348; encontrado (ESLFTMS, $[M+H]^{1+}$), 522.22365.

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Ejemplo 33B: N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-dimetilbencil)-N^5-hidroxi-L-glutamamida

MS (ESI) *m/z* 460.2; MS (ESI) *m/z* 919.4; HRMS: calculado para $C_{27}H_{29}N_3O_4$ +H+, 460.22308; encontrado (ESI_FTMS, $[M+H]^{1+}$), 460.22328.

Ejemplo 33C: N^2-(1,1'-bifenil-4-ilcarbonil)-N^5-hidroxi-N^1-[2-(3-metoxifenil)etil]-1-glutamamida

MS (ESI) *m/z* 476.2; MS (ESI) *m/z* 951.4; HRMS: calculado para $C_{27}H_{29}N_3O_5$ +H+, 476.21800; encontrado (ESI_FTMS, $[M+H]^{1+}$), 476.21792.

Ejemplo 33D: N^2-(1,1'-bifenil-4-ilcarbonil)-N^5-hidroxi-N^1-[3-(trifluorometoxi)bencil]-L-glutamamida

MS (ESI) *m/z* 516.2; MS (ESI) *m/z* 1031.4; HRMS: calculado para $C_{26}H_{24}F_3N_3O_5$ + H+, 516.17408; encontrado (ESI_FTMS, $[M+H]^{1+}$), 516.17389.

Ejemplo 34: Selección de Fluorescencia In vitro para Inhibidores de Agrecanasa-1

Materiales y Métodos

Este ensayo es una selección preliminar de inhibidores de agrecanasa-1 potenciales en once concentraciones para determinar su capacidad para inhibir la segmentación de un

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péptido fluorescente (Abz-TEGEARGSVI-Dap(Dnp)-KK). Un fluorímetro GeminiXS (Molecular Devices) se enciende y la temperatura se establece a 30 °C ~ 30 min antes de establecer el ensayo. Se utilizan los siguientes amortiguadores: 50 mM HEPES, pH 7.5; 100 mM NaCl; 5 mM $CaCl_2$; 0.1 % CHAPS; y 5% de glicerol. La fuente de enzima en el ensayo es agrecanasa-1 humana recombinante purificada (rAggl), utilizada en 5 µg/ml (concentración final en el ensayo). El sustrato utilizado en el ensayo es el péptido (AnaSpec, MWT= 1645.8, almacenado a 4° C). Una solución madre del péptido se prepara en 2 mg/ml 100 % DMSO. La absorbancia en 354 nm (ϵ=18172 $M^{-1}Cm^{-1}$) se mide para determinar la concentración exacta de la solución madre. La solución madre se diluye luego a 62.5 µM en amortiguador. El 100 % de solución madre DMSO no utilizada se almacena a -80° C. La concentración final del sustrato en el ensayo es 25 µM. Las soluciones de inhibidor se preparan en 100 % DMSO con una concentración de partida de 10X, y se desarrollan diluciones en serie (el duplicado) a lo largo de la placa de dilución en 100 % DMSO.

El ensayo se desarrolla como sigue: se disponen placas de 96 pozos de tal manera que la columna final de los pozos se utiliza para controles. El volumen de reacción total de cada pozo es 100 µl. Cada compuesto se ensaya por duplicado, se agrega amortiguador a la placa de 96 pozos completa (30 µl/ pozo). Se diluye rAggl para 25 µg/ml de amortiguador justo antes de la adición en la placa, y se agrega a los pozos en 20 µl/pozo. Se agrega 10 µl/ pozo de inhibidores 10x a los pozos apropiados de la placa de trabajo, excepto para los

pozos de control, a los que se agrega 10 µl/ pozo de un compuesto de control de referencia 10X o 100% DMSO. La mezcla se incuba durante 10-15 min a 30° C. Luego se agrega 40 µl/pozo de 62.5 µM de sustrato de péptido a los pozos apropiados.

Resultados

La reacción se monitorea durante 30-40 min a 30 °C, con λex = 340 nm y λ em = 420nm. La fluorescencia es lineal durante este tiempo y la pendiente de la línea (Vmax/sec) representa la velocidad de reacción inicial, v. La tasa máxima de segmentación del sustrato se determina en la ausencia de inhibidor. El porcentaje de inhibición de actividad en la presencia del inhibidor se calcula como sigue: % inhibición = (1- v (Velocidad, RFU/sec)/Velocidad máxima (RFU/sec))*100. El IC_{50} se obtiene al ajustar la velocidad inicial, V, o % de inhibición en cada concentración de inhibidor para la siguiente ecuación: y = (a-d)/($^{1+}$ C/ IC_{50})^n)+d. Los resultados del ensayo se muestran en las Tablas 1, 2, y 3 adelante.

Este modelo describe una curva sigmoidal con una línea base ajustable, a. y es el porcentaje de inhibición o tasa inicial de reacción, C es la concentración de inhibidor bajo ensayo. A es la respuesta limitante cuando C se aproxima a cero. Como C se incrementa sin límite, y tiende hacia su límite inferior, d. y es el punto medio entre las asíntotas superior e inferior cuando C= IC_{50}. n es el coeficiente de Hill. El signo de n es positivo cuando la respuesta se incrementa con

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el aumento de la dosis y es negativa cuando decrece la respuesta con incremento de dosis (inhibición). (Ver, Knight, CG. Methods Enzymol. 1995, 248, 18-34; Knight, CG. et al., FEBS Lett. 1992, 296, 263-266; Jin, G. et al., Anal. Biochem. 2002, 302, 269-275).

Ejemplo 35: Selección de fluorescencia in Vitro para Inhibidores de Agrecanasa-2

Materiales y métodos

Se utiliza un ensayo continuo en el que el sustrato es un péptido sintético que contiene un grupo fluorescente que se apaga mediante transferencia de energía. La segmentación del péptido mediante la enzima resulta en un incremento grande en la florescencia. La velocidad inicial para esta reacción se compara con la velocidad inicial para las reacciones que contienen inhibidores con el fin de evaluar la potencia de moléculas pequeñas. La fuente de esta enzima en este ensayo es agrecanasa-2 humana recombinante purificada en Wyeth Research (Biological Chemistry, Cambridge). Más específicamente, la forma utilizada se denomina como Ag2t-Phe_{628}-Strep (PF= 41,737). Esta forma se trunca con relación a la enzima de longitud completa y contiene una etiqueta de afinidad. Las alícuotas de esta enzima se almacenan a 80°C en 25mM Tris (pH 8.0), 100mM NaCl, 5mM $CaCl_2$, 10μM $ZnCl_2$, 10% de glicerol. El sustrato en el ensayo es un péptido sintético que se diseña después de una porción de brevican, uno de los sustratos de ocurrencia natural de agrecanasa-2. Este péptido

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contiene el grupo fluorescente 2-aminobenzoil (Abz) que se apaga mediante transferencia de energía a un grupo 2,4-dinitrofenilo (Dnp). El péptido (masa= 1740) es >95% puro con base en análisis HPLC y tiene la secuencia: Abz TESESRGAIY-Dap(Dnp)-KK-NH_2. Las soluciones madre de los sustratos se prepara con agua MilliQ y las alícuotas se almacenan a 80°C. La concentración d este sustrato madre se determina espectrofotométricamente utilizando el coeficiente de extinción en 354nm de 18,172 M^{-1} cm^{-1}. La V_{max} y K_m para esta reacción enzima/sustrato se determina por ser insensible al DMSO hasta por lo menos 10% (v/v). El amortiguador de ensayo (pH 7.4) consiste de 50mM Hepes, 100mM NaCl, 5mM $CaCl_2$, 0.1% CHAPS, 5% de glicerol.

Cada pozo de los 96 pozos o placas de 384 pozos contienen una reacción que consiste de amortiguador de ensayo, Agg-2 purificado (diluido con amortiguador de ensayo), y concentraciones que varían de inhibidor (preparado mediante dilución en serie en DMSO en placas de polipropileno de 96 pozos). Las placas se incuban luego a temperatura ambiente durante 10 minutos. Las reacciones enzimáticas se inician al agregar el sustrato a una concentración final de 25 μM y se mezclan al pipetear en forma ascendente y descendente. Las velocidades iniciales de las reacciones de segmentación se determinan a temperatura ambiente con un lector de placa fluorescente inmediatamente después del sustrato. Los ensayos Agg-2 se corren en un Tecan Safire con las siguientes configuraciones de longitud de onda: excitación - 316nm, ancho de banda 12nm; emisión - 432nm, ancho de banda 12nm.

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Resultados

Se genera una gráfica de tiempo vs. RFU, que representa la curva de progreso de la reacción. Se determina la pendiente para la porción de la curva de progreso que es casi lineal. Esta pendiente (RFU/min) es la velocidad inicial de la reacción. Las gráficas de la concentración de inhibidor Vs. La velocidad de segmentación inicial se ajustan a la siguiente ecuación: $y = Vmax*(1-(x^n / (K^n + x^n)))$, por lo cual x = concentración de inhibidor, y = velocidad inicial, V_{max} = velocidad inicial en la ausencia de inhibidor, n = factor de pendiente, y K = IC_{50} para la curva de inhibición. Los resultados de ensayos se muestran en las tablas 1, 2, y 3 adelante.

Ejemplo 36; Ensayo de fluorescencia in Vitro de actividad MMP-13

Materiales y métodos

Se utiliza un ensayo continuo en el que el sustrato es un péptido sintético que contiene un grupo fluorescente (7-metoxicoumarin; Mca), que se apaga mediante transferencia de energía a un grupo 2,4-dinitrofenilo. Cuando el péptido se cliva por MMP, se observa un incremento grande en la fluorescencia. La fuente de la enzima en el ensayo es el dominio catalítico humano recombinante del MMP-13 (165 aminoácidos, 104-268 residuos, 19kDa) preparado en Wyeth-

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Research en Cambridge. El sustrato utilizado es el péptido Mca-PQGL-(3-[2,4-dinitrofenil]-L-2,3-diaminopropionil)-AR-OH. El amortiguador de ensayo consiste de 50mM Hepes (pH 7.4), 100mM NaCl, 5mM $CaCl_2$, y 0.005% Brij-35. Cada pozo de las placas de 96 pozos contiene una mezcla de reacción de 200μL que consiste de amortiguador de ensayo, MMP purificado (concentración final de 0.5nM, preparado al diluir con el amortiguador de ensayo), y concentraciones variadas de inhibidor (preparadas mediante dilución serial de un inhibidor dado en DMSO en placas de polipropileno de 96 pozos). Las placas luego se incuban a 30°C durante 15 minutos. Las reacciones enzimáticas se inician al agregar el sustrato a una concentración final de 20μM, y mezclar 10 veces con una pipeta. La concentración final de DMSO en el ensayo es 6.0%. La velocidad inicial en la reacción de segmentación se determina en 30°C de temperatura con un lector de placa de fluorescencia (filtro de excitación de 330nm y filtro de emisión de 395nm) inmediatamente después de adición del sustrato.

Resultados

Las gráficas de la concentración de inhibidor vs. el porcentaje de inhibición se ajustan a la siguiente ecuación: $y = (a-d)/[1+(x/c)^b]+d$, una curva sigmoidal general con pendiente Hill, a a d. x es la concentración de inhibidor bajo ensayo, y es el porcentaje de inhibición, a es la respuesta limitante cuando x se aproxima a cero. Como x se incrementa sin límite, y tiende hacia su límite d. c es el

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punto de inflexión (IC_{50}) para la curva. Esto es, y es el punto medio entre las asíntotas inferior y superior cuando x=c. b es el factor de pendiente o coeficiente de Hill. (Ver, Knight, CG. et al., FEBS Lett. 1992, 296, 263-266). Los resultados del ensayo se muestran en las Tablas 1, 2 y 3 adelante.

Ejemplo 37: Ensayo de fluorescencia in Vitro de actividad MMP- 14

Materiales y materiales

Se utiliza un ensayo continuo en el que el sustrato es un péptido sintético que contiene un grupo fluorescente (7-metoxicoumarin; Mca), que se apaga mediante transferencia de energía a un grupo 2,4-dinitrofenilo. Cuando el péptido se segmenta por MMP, se observa un gran incremento en fluorescencia. La fuente de enzima en el ensayo es el dominio catalítico humano recombinante del MMP-14 (177 aminoácidos que corresponde a Tyr89-Gly265 de enzima humana madura; 20 kDa; Chemicon International, Inc. (catálogo número CC1041)). El sustrato utilizado es el péptido Mca-PQGL-(3-[2,4-dinitrofenil]-L-2,3-diaminopropionil)-AR-OH. El amortiguador de ensayo consiste de 50mM Hepes (pH 7.4), 100mM NaCl, 5mM $CaCl_2$, y 0.005% Brij-35. Cada pozo de las placas de 96 pozos contiene una mezcla de reacción de 200μL que consiste de amortiguador de ensayo, MMP (concentración final de 25ng/ml, preparado al diluir con el amortiguador de ensayo), y concentraciones variadas de inhibidor (preparadas mediante

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dilución serial de un inhibidor dado en DMSO en placas de polipropileno de 96 pozos). Las placas luego se incuban a 30°C durante 15 minutos. Las reacciones enzimáticas se inician al agregar el sustrato a una a concentración final de 20μM, y mezclar 10 veces con una pipeta. La concentración final de DMSO en el ensayo es 6.0%. La velocidad inicial en la reacción de segmentación se determina en 30°C de temperatura con un lector de placa de fluorescencia (filtro de excitación de 330nm y filtro de emisión de 395nm) inmediatamente después de adición del sustrato.

Resultados

Las gráficas de la concentración de inhibidor vs. el porcentaje de inhibición se ajustan a la siguiente ecuación: $y = (a-d)/[1+(x/c)^b]+d$, una curva sigmoidal general con pendiente Hill, a a d. x es la concentración de inhibidor bajo ensayo, y es el porcentaje de inhibición, a es la respuesta límite cuando x se aproxima a cero. Como x se incrementa sin límite, y tiende hacia su límite d. c es el punto de inflexión (IC_{50}) para la curva. Esto es, y es el punto medio entre las asíntotas inferior y superior cuando x=c. b es el factor de pendiente o coeficiente de Hill. (Ver, Knight, CG. et al., FEBS Lett. 1992, 296, 263-266). Los resultados del ensayo se muestran en las Tablas 1, 2 y 3 adelante.

Ejemplo 38: Ensayo de fluorescencia in Vitro de actividad MMP-2

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Materiales y métodos

Se utiliza un ensayo continuo en el que el sustrato es un péptido sintético que contiene un grupo fluorescente (7-metoxicoumarin; Mca), que se apaga mediante transferencia de energía a un grupo 2,4-dinitrofenilo. Cuando el péptido se segmenta por MMP, se observa un incremento grande en la fluorescencia. La fuente de enzima en el ensayo es el MMP-2 (66 kDa; Oncogene Research Products (catálogo número PF023 de Calbiochem)). El sustrato utilizado es el péptido Mca-PQGL-(3-[2,4- dinitrofenil]-L-2,3-diaminopropionil)-AR-OH. El amortiguador de ensayo consiste de 50mM Hepes (pH 7.4), 100mM de NaCl, 5mM de $CaCl_2$, y 0.005% Brij-35. Cada pozo de las placas de 96 pozos contiene una mezcla de reacción de 200μL que consiste de amortiguador de ensayo, MMP (concentración final de 25ng/ml, preparado al diluir con el amortiguador de ensayo), y concentraciones variadas de inhibidor (preparadas mediante dilución serial de un inhibidor dado en DMSO en placas de polipropileno de 96 pozos). Las placas luego se incuban a 30°C durante 15 minutos. Las reacciones enzimáticas se inician al agregar el sustrato a una a concentración final de 20μM, y mezclar 10 veces con una pipeta. La concentración final de DMSO en el ensayo es 6.0%. La velocidad inicial en la reacción de segmentación se determina en 30°C de temperatura con un lector de placa de fluorescencia (filtro de excitación de 330nm y filtro de emisión de 395nm) inmediatamente después de adición del sustrato.

Resultados

Se ajustan las gráficas de la concentración de inhibidor vs. el porcentaje de inhibición a la siguiente ecuación: $y = (a-d)/[1+(x/c)^b]+d$, una curva sigmoidal general con pendiente Hill, a a d. x es la concentración de inhibidor bajo ensayo, y es el porcentaje de inhibición, a es la respuesta limitante cuando x se aproxima a cero. Como x se incrementa sin límite, y tiende hacia su límite d. c es el punto de inflexión (IC_{50}) para la curva. Esto es, y es el punto intermedio entre las asíntotas inferior y superior cuando x=c. b es el factor de pendiente o coeficiente de Hill. (Ver, Knight, CG. et al., FEBS Lett. 1992, 296, 263-266). Los resultados del ensayo se muestran en las Tablas 1, 2 y 3 adelante.

Ejemplo 39: Modelo de cartílago articular in vitro para la inhibición de la degradación de proteoglicano mediante compuestos de moléculas pequeñas: cultivos de explantes de cartílago articular de bovinos

Este procedimiento in Vitro se utiliza para evaluar el efecto y las potencias relativas de compuestos de molécula pequeñas para inhibir la degradación de proteoglicano en cartílago articular tratado con Interleuquina 1 alfa (IL- 1α). El tratamiento del cartílago articular con IL 1α induce la expresión de una cascada de enzimas que inicia la degradación de matriz del cartílago. Este ensayo se utiliza para seleccionar compuestos de molécula pequeña que inhiben la

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actividad de enzima y protegen la degradación de matriz de cartílago.

Materiales y Métodos

Cartílago articular: se desinfectan articulaciones del metacarpo de bovino con 10% de Wescodyne seguido por 70% de etanol. Se preparan discos de cartílago articular de 6mm y se enjuagan una vez en PBS y medio, respectivamente. Los discos se cultivan en un frasco de agitación con medio libre de suero durante 5 días para equilibrio con un cambio de medio. Compuestos de molécula pequeña: soluciones madre de compuestos de molécula pequeña de ensayo (usualmente en 5mg/ml) se preparan en DMSO. Las soluciones de trabajo se diluyen con DMSO y varían generalmente de 0.1 µg/ml a 10 ug/ml. Las soluciones madre de DMSO se almacenan a 20°C. Medio de cultivo de explante de cartílago articular: DMEM, 2mM glutamax, 100 U/ml de antibiótico y antimicótico, 50 µg/ml de ascorbato y 10 mM Hepes (pH-7.0). Solución de dimetil metileno azul (DMMB)- contenido de proteoglicano: 1L-16mg DMMB, 10ml 100% etanol, 29.5ml de 1M NaOH, 3.5 ml de 98% de ácido fórmico y agua a IL. Sal de sulfato de sodio condroitina: diluciones seriales 1.56-200 ug/ml.

Para el cultivo de explante, los discos de cartílago se cultivan en medio libre de suero durante 48 h o más. Los discos se pesan y transfieren a una placa de 96 pozos, un disco por pozo. 0.2 ml de medio que contiene 5ng/ml de IL-I y diferentes concentraciones de los compuestos se agregan a

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cada pozo, con tres pozos ubicados para cada tratamiento. El medio se recolecta en los días 1, 2, y 3 y se reemplazan de acuerdo con esto.

Para en ensayo DMMB, se diluyen muestras de medio acondicionado (CM) con medio. 10 ul de cada muestra diluida o estándar se agregan en duplicado en una placa de 96 pozos y se agrega solución de 200μl de DMMB en cada pozo. Se mide la absorbancia en 520nm para cada pozo. Los contenidos de proteoglicano en CM se calculan diariamente.

Resultados

Los contenidos de proteoglicano se expresan como ug por mg de cartílago. El efecto inhibidor de los compuestos se expresa como porcentaje. (ver, Tortorella, M.D. et al., Science 1999, 284, 1664-1666). Los resultados del ensayo se muestran en las tablas 1, 2, y 3 adelante.

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TABLA 1

Ejemplo	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1	bovino	bovino
8SSSS	>200,000								
7	150		1,800	~ 13,000	3,000	~13,000	>100,000	61	28
8C	110		1,200	~50,000	6,000	~25,000	>100,000	68	34
8B	460		1,900	~50,000	5,600	~25,000	>100,000	54	22
8A	150		900	~40,000	4,400	~25,000	>100,000	75	29
11	110		~ 800	~ 5,000	~ 1,000	~ 2,000	~ 2,000	78	52
12A	700		~ 5,000	~ 6,000	~ 2,000	~ 2,000	~ 2,000	41	18
12B	35000								
8D	220		2,800	~25,000	4,400	17,000	>100,000	67	27
8E	90		746	~25,000	3,700	~25,000	> 200,000	79	34
8NNNNNN	~40,000								
13B	~50,000								
8F	30	12	304	~22,000	5,630	~25,000	> 200,000	81	56
17VV	7900								
13A	1500		~67,000	>100,000	~67,000	> 100,000	>100,000	37	18
13C	9600								
13D	750		~26,000	>200,000	>200,000	>100,000	>100,000	51	25
13E	~ 25,000								
13F	~ 200								
8G	80		614	~50,000	~50,000	~25,000	>100,000	76	39
8OOOOOO	670								
8H	200		266	~50,000	3,310	~25,000	>100,000	85	67
8I	500								
12E	1800								
12C	25000								
12D	> 100,000								
8K	300								

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Ejemplo	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1	bovino	bovino
8L	55		189	~50,000	10,500	21,500	> 100,000	87	79
8J	360								
8M	120		856	~50,000	8,000	13,000	> 100,000	85	17
8N	290								
8O	75	82	1,300	31,400	5,000	~ 22,000	no inh	69	34
8P	290								
8Q	11	31	400	37,300	6,100	~ 22,000	no inh	66	24
8R	16	5	50	42,400	10,400	~ 22,000	no inh	86	78
8S	150	245	1,300	> 200,000	3,130	~25,000	no inh	51	40
8T	300							51	20
8U	200							63	26
8V	160		1,100	~ 67,000	3,430	~ 30,000	> 100,000	73	45
8W	75		971	~ 22,000	~ 2,500	~25,000	no inh		
8X	100		1,100	~ 67,000	7,000	~ 25,000	no inh		
8Y	50		520	~ 67,000	5,534	~ 25,000	no inh		
8Z	80		680	~ 67,000	3,820	~ 25,000	no inh		
8BB	74		650	19,000	2,300	~ 25,000	no inh		
8AA	370								
33D	< 10		13.4	52	3.3	73.6	~ 1,560		
33C	< 10		25	29	4.5	110	1,500		
Control (33A)	<10		2.6	32	4.7	112	1,750		
8CC	22	19	121	~ 22,000	5,655	~ 25,000	no inh	94	71
13G	~2500								
8DD	94		930	~ 22,000	4,580	16,200	no inh	89	50
14	60% @ 16,700								
15A	> 22,000								
15B	67 % @ 7,500								
15C	50 % @ 7,500								
15D	86% @ 7,500								
15E	3500								
33B	< 30								
8PPPPPP	>33,000								
23	> 6000								
24A	1100								
24B	~2200								
24C	~300								
20	~ 22,000								
21A	2500-7500								
21B	~ 6700								

Ejemplo	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1	bovino	bovino
21C	no inh								
21D	no inh								
22C	> 50,000								
8FFF	200		1000						
8GGG, step D	100							57	12
8AAAA	100								
8DDDD	110								
8HHHH	200								
8XX	300								
8FF	26	28						86	50
17WW	no inh								
17XX	no inh								
17YY	2000								
17ZZ	200								
17AAA	no inh								
8YY	530		4500						
8ZZ	210								
8AAA	48	44						83	55
8EE	200								
15F	600								
15G	2200								
15H	200								
6A	150		740	>50,000	29800	> 200,000	> 50,000		
8HH	160								
8II	44	39						75	40
8QQQQQQ	690								
17BBB	900								
8III	120								
8NNN	100	219	1750	14,000	> 10,000	>50,000	> 50,000	60	0
8JJJ	54	54	300	30,000	>20,000	>200,000	>200,000	74	26
8JJ	45	33	1100	17,000	27,000	>200,000	>200,000	70	17
10M	43	54	1100	~20,000	>20,000	>200,000	>50,000	67	35
10N	19	28	970	>50,000	7600	>200,000	>200,000	65	24
8OO	<30	6	44	>50,000	>20,000	>200,000	>200,000	87	40
22A	1000								
22B	200								
8KK	180								
8LL	55		990	24,000	50,000	200,000	200,000	40	0
10R	77	187	1900	>20,000	>20,000	>200,000	>50,000	41	0
8BBB	32	130	700	>50,000		no inh	> 200,000	35	0
8CCC	100							74	26
8ZZZ	100		1600	no inh	13,000	> 200,000	>50,000	72	34
8KKK	120		2000						

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Ejemplo	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1	bovino	bovino
10C	240		>5000						
10E	370								
10F	130		>30000						
10D	480		3200						
10G	1000		4400						
8BBBB	100							40	0
8OOO	280		1000						
8LLL	230								
8PPP	130								
8QQQ	330								
8EEE	7900								
8MM	58	126	980						
9	200								
10A	840		2100						
10J	260								
10K	380		>100000						
10L	130		2000						
10B	150								
8MMM	40		500						
8RRR	82		680						
10H	300								
8SSS	64		470	>50,000	10300				
10O	470								
8UUU	61	60	660	~50,000	8900	>200,000	no inh		
10P	700								
10Q	98		3000	~50,000		>50,000	no inh		
8PP	<30	10	85	~50,000	6000	>66,600	> 200,000		
8NN	<30	14	133	~50,000	9000	no inh	>200,000		
8VVV	30	38	420	~50,000	5600	>66,600	no inh		
8TTT	>10000								
6C	150								
8DDD	300								
6B	300								
8SS	100		800	~50,000	12400	>66,600	no inh		
8TT	300								
8UU	200								
8WW	70		350	~50,000	13300	> 66,600	no inh		
8VV	100		1900	~50,000	9100	> 66,600	no inh		
8XXX	30		930	~50,000	7900	> 200,000	no inh		
8WWW	36		840	~200,000	7400	> 200,000	no inh		
8YYY	100		1600	> 50,000	9400	> 200,000	no inh		
8GGGG	30		160	>50,000	18600	no inh	no inh		

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Ejemplo	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1	bovino	bovino
8FFFF	3600								
10I	320								
8RRRRRR	3600								
8KKKK	<30	4							
8LLLL	no inh								
8MMMM	47	57							
8IIII	<30	9							
8JJJJ	>50000								
8NNNN	3400								
8OOOO	52	60							
8PPPP	>50000								
8QQQQ	9600								
8RRRR	122								
8SSSSSS	146								
8TTTTTT	17300								
1	900								
2	111								
3	12700								
4	1100								
5	1800								
8EEEE, step D	400								
8UUUUUU	4000								
26	5000								
27	400								
28	400								
29	3000								
30	500								
31	1000								
6D	45								
6E	56								
8VVVVVV	46								

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Tabla 2

Ejemplo	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1
8TTTT	> 17,000		> 22,000				
8UUUU	> 17,000		~ 67,000				
8VVVV	> 17000		> 67,000				
8WWWW	8300		> 67,000				
8XXXX	> 50,000		>200,000				
8YYYY	1500		>200,000				
8ZZZZ	> 17000		> 22,000				
8AAAAA	372		410				
8BBBBB	> 17000		20900				
8CCCCC	107		11000				
8DDDDD	315		1100				
8EEEEE	> 50000		>200,000				
8FFFFF	92		710	>100,000			
8GGGGG	> 50,000						
8HHHHH	357						
8IIIII	813		1900				
8JJJJJ	191		1100				
8KKKKK	> 50,000		> 22,000				
8LLLLL	> 17,000		>200,000				
8MMMMM	20000		~ 22,000				
8NNNNN	1200		1,893 +/- 76				
8OOOOO	> 50,000		> 200,000				
8PPPPP	157		2967				
8QQQQQ	108		1165				
8RRRRR	129		2905				
8SSSSS	208		2470				
8TTTTT	389		2011				
8UUUUU	317		2119				
8VVVVV	221		1558				
8WWWWW	> 17,000		> 67,000				
8XXXXX	246		1450				
8YYYYY	87		2800	~ 20,000			
8ZZZZZ	<30		63	>100,000			
16	< 30 nM		467				
17A	116		1123				
17B	204		1020				
18D	4400		> 22,000				
17C	< 30 nM		80				
17D	> 17,000		>				

Ejemplo	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1
	nM		200,000				
17E	251		1040				
12F	~ 3,000 nM		3,000 - 8,000				
17F	1700		~ 8,300				
17G	1600		3,000 - 8,000				
17H	1000		~ 22,000				
8AAAAAA	534		1759	-			
17I	< 30		217 +/- 8	~100,000			
17J	~5,600		~ 30,000	-			
17K	1200		~ 3,700	-			
17L	133		226	-			
18E	2200		> 11,000	-			
17M	~ 310		> 11,000	-			
17N	40		42	11,200 +/- 1,200			
8MMMMMM	550		5100	-			
8BBBBBB	470		2671	-			
18F	> 67,000		> 67,000	-			
17O	8500		~ 22,000	-			
17P	126		58	-			
17Q	~ 13,000		> 30,000	-			
17R	73		142	6,000 +/- 400			
18	49		50	~ 1,600 nM			
19A	930		1020				
19B	3200		590				
8CCCCCC	2400		> 22000				
17S	4600		10100				
17T	3200		7200				
17U	1800		~ 6700				
19C	140 +/- 20		75				
17V	90		1800				
17W	> 25,000		~ 67000				
17X	2000		~ 22000				
8DDDDDD	2400		> 22000				
17Y	<30		156				
19D	210		223				
19E	49		1120				
17Z	170		3140				
17AA	3500		5700				

Ejemplo	Agg1 IC_{50} (nM)	K_i (nM)	Agg 2 IC_{50} (nM)	MMP-13	MMP-2	MMP-14	MMP-1
17BB	3600		2900				
17CC	2900		2970				
17DD	<30nM		1190				
17EE	<30nM		194				
17FF	690		13900				
17GG	34		113				
17HH	2200		6320				
17II	~ 1000-3000		~ 10,000				
17JJ	2400		19454				
15I	430		1593				
15J	510		~ 3,125				
12G	> 25000		11700				
12H	1200		1635				
12I	> 25000		> 20,000				
17KK	> 25000		> 67,000				
19F	68		163				
17LL	87		1193				
17MM	46		2707				
19G	270		146				
19H	69		158				
18G	~ 8300						
17NN	200		729				
8EEEEEE	5000						
17OO	<30		1677				
8FFFFFF	3900		18131				
8GGGGGG	4200						
8HHHHHH	38		46				
8IIIII	2900		11908				
8JJJJJJ	300		943				
8KKKKKK	350		1674				
17QQ	> 25,000		~22000				
12J	~ 8,000		~22000				
12K	~ 25,000		>22000				
12L	~ 22,000		>22000				
17RR	<30		26				
17SS	450		3959				
17TT	120		173				
8LLLLLL	>25000		>100000				
15Y	220		841				
15Z	1400		6036				
15AA	44		327				
15BB	53		527				
17UU	<30		39				

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Tabla 3

Ejemplo	Agg1 IC_{50} (nM)	K_i Agg1 (nM)	Agg 2 IC_{50} (nM)	K_i Agg2 (nM)	MMP -13	MMP-2	MMP -14	MMP-8	MMP-12
8WWWWWW	<03	7.1	50	72		2600		1000	5800
8XXXXXX	<30	<3	20	60		7500		4100	1600
8YYYYYY	<30	13.5	30	160		4700		737	365
8ZZZZZZ	<30		120						
8AAAAAAA	80		550						
8BBBBBBB	110		1000						
8CCCCCCC	50		680						
8DDDDDDD	<30		220						
8EEEEEEE	37		510						
8FFFFFFF	200		4200						
8GGGGGGG	60		160						
8HHHHHHH	50		180						
8IIIIII	<30		42						
8JJJJJJ	<30		53						
8KKKKKKK	<30		<30						
8LLLLLLL	228		3360						
8MMMMMMM	198		614						
8NNNNNNN	<30	<3	<30	37		2150		1210	680
8OOOOOOO	<30		100-400						
8PPPPPPP	3116		48% 16700						
8QQQQQQQ	NT		NT						
8RRRRRRR	70-210		48% 1200						
8SSSSSSS	57	22	230	356					
8TTTTTTT	707		20% 11000						
8UUUUUUU	<30	<3	60	60		5180		2030	410
8VVVVVVV	<30	7	51% 140	305		570		410	770
8WWWWWW	<30	<3	50	42		1080		370	630
8XXXXXXX	<30	4.5	20-70	56					
8YYYYYYY	<30	27	200-600	197					
8ZZZZZZZ	<30	12.7	200-600	290					
8AAAAAAAA	<30	86	600-1800	1147					
8BBBBBBBB	300		200-600						
8CCCCCCCC	140		5200						
8DDDDDDDD	50		1000						
8EEEEEEEE	<30	3.8	60-200	79					
8FFFFFFFF	<30		200						
8GGGGGGGG	40		3400						
8HHHHHHHH	60		3000						
8IIIIIII	65% 200		80-270						
8JJJJJJJ	<30		800-2500						
8KKKKKKKK	70		270-800						
8LLLLLLLL	<30	<3	60-200	156					
8MMMMMMMM	<30	<3	60-200	38					
8NNNNNNNN	<30	<3	70-200	151					
8OOOOOOOO	<30		200-600						

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Ejemplo	Agg1 IC_{50} (nM)	K_i Agg1 (nM)	Agg 2 IC_{50} (nM)	K_i Agg2 (nM)	MMP -13	MMP-2	MMP -14	MMP-8	MMP-12
8PPPPPPPP	<30		200-600						
8QQQQQQQQ	<30		3300						
8RRRRRRRR	57% 70		7200						
8SSSSSSSS	<30	5.4	70-200	51					
8TTTTTTTT	20-70	37.6	100-300	359					
8UUUUUUUU	100		700						
8VVVVVVVV	60% 16700		50% 50000						
8WWWWWWWW	20-70	40.6	100-300	526					
8XXXXXXXX	100		1700						
8YYYYYYYY	<30	6.2	100-300	143					
8ZZZZZZZZ	20-70		9900						
8AAAAAAAA	<30	6.7	98	45					
8BBBBBBBB	<30	11.5	100-300	681					
8CCCCCCCC	<30		900						
8DDDDDDDD	2400		50% 7400						
8EEEEEEEE	1200		50% 2500						
8FFFFFFFF	270		62% 25000						
8GGGGGGGG	30% 8300		28% 25000						
8HHHHHHHH	<30		500						
8IIIIIIII	300-900		5% 2500						
8JJJJJJJJ	25% 25000		10% 25000						
8KKKKKKKK	18% 25000		10% 25000						
8LLLLLLLL	<30		>300						
8MMMMMMMM	<30	<3	30-100	87					
8NNNNNNNN	<30	8.3	30-100	89					
8OOOOOOOO	<30	2.7	~30	66		718		349	372
8PPPPPPPP	<30	11.5	30-300	126		7240		2550	2890
8QQQQQQQQ	>900		>8300						
8RRRRRRRR	>8300		100000						
8SSSSSSSS	<30	8.8	200	157					
8TTTTTTTT	<30	6.7	59	54					
8UUUUUUUU	<30	6.9	83	75					
8VVVVVVVV	<30	4.5	77	81					
8WWWWWWWW	>25000		>100000						
8XXXXXXXX	<30	18.2	25	71.6		2610		1790	597
8YYYYYYYY	<30	39.6	250	349		26500		13200	3710
8ZZZZZZZZ	<30	4.7	30-90	123		8280		2440	2860
8AAAAAAAA	<30	28.9	100-300	204		6970		2230	2240
8BBBBBBBB	22000		>200000						
8CCCCCCCC	1040		7400						
8DDDDDDDD	<30	27.2	90	218		4000		763	628
8EEEEEEEE	<30	23.2	80	180		6400		2500	1070
8FFFFFFFF	>400		>2700						
8GGGGGGGG	<30	42	>300	723		1300		>5000	>10,000
8HHHHHHHH	<30	11.7	>100	405		8000		3400	>10,0

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Ejemplo	Agg1 IC_{50} (nM)	K_i Agg1 (nM)	Agg 2 IC_{50} (nM)	K_i Agg2 (nM)	MMP -13	MMP-2	MMP -14	MMP-8	MMP-12
									00
8IIIIIIIII									
15O	52		3132						
15P	<30		255						
15K	<30		379						
15L	47		413						
15M	<30		789						
15N	91		103						
15U	53% 100		600						
15V	47% 40		700						
15Q	158		1939						
15R	560		48% 11000						
15S	30% 1850		41% 33000						
15U	53% 1000		30% 11000						
15W	56% 1900		59% 11000						
15X	46% 1900		52% 11000						

Ejemplo 40: Inhibidores de agrecanasa en estudios de explantes y cartílagos osteoartríticos humanos y efecto en el metabolismo del agrecán en cartílago osteoartrítico de humanos

La pérdida de la matriz de cartílago en la osteoartrítis (OA) se asocia con la pérdida incrementada del colágeno tipo II por colagenasas y pérdida de agrecán por agrecanasas. El agotamiento del agrecán es uno de los cambios prematuros observados en osteoartrítis (Lohmander, LS et al., Arthritis & Rheum 1993, 36,1214-1222). El Agrecán es un sulfato de condroitina y el proteoglicano que lleva sulfato de keratan. La Agrecanasa 1 y Agrecanasa 2 segmentan en agrecán dentro del dominio interglobular en el sitio agrecanasa entre los residuos GIu^{373} y Ala^{374} (Sandy, JD et al., J Clin Invest.

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1992, 89, 1512-1516). La segmentación del agrecán por agrecanasa resulta en la liberación de una gran cantidad de glicosaminoglicano sulfatado (sGAG)-que contiene fragmentos de agrecán que son difusos de la matriz de cartílago. Los anticuerpos de neoepítopos se han generado para reconocer estas agrecanasas generadas por fragmentos de agrecán (Hughes, CE et al., Biochem J. 1995, 305, 799-804). Los fragmentos de agrecán en el fluido sinovial OA e inflamatorio se han reportado por ser generados por segmentación en el sitio agrecanasa (MaIf ait, A-M et al., J Biol Chem. 2002, 277, 22201-22208). La inhibición de la actividad agrecanasa es un objetivo terapéutico atractivo para OA. En este ejemplo, investigamos los efectos de un inhibidor agrecanasa selectivo sobre en el sino de la existencia y nuevamente el agrecán sintetizado en cartílago OA humano.

Materiales y Métodos

Cultivo de explante de cartílago OA humano: Tejidos descartados de pacientes con reemplazo con sentido de rodilla se obtienen de New England Baptist Hospital (Brookline, MA) en salina amortiguada con fosfato estéril (PBS) después de 2-4 horas post-cirugía. Se cultivan láminas de cartílago de los especimenes de rodilla y se lavan varias veces en PBS. Las láminas de cartílago se cortan en piezas apropiadas (6-8 mm) y se enjuagan en PBS y luego en medio y se cultivan adicionalmente durante días adicionales como explantes de cartílago. El medio consiste de Medio Eagle modificado de Dulbecco (DMEM, JRH Biosciences, Lenexa, KS), 50μg/ml de

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ácido ascórbico (Wako, Osaka, Japón), 10mM HEPES, pH 7.0 (Mediatech, Herndon, VA), 2mM L-glutamina (Mediatech), 100 U/ml de solución antibiótico-antimicótica (Mediatech).

Compuestos de ensayo: los compuestos de ensayo se describen en los ejemplos 800, 8NNNNNNN, y 8WWWWWWW. Las soluciones madre de los compuestos se preparan en 1 mg/ml en DMSO, se dividen en alícuotas y se almacenan a -20 °C. Las soluciones de trabajo de los compuestos se hacen en DMSO y se agrega al cultivo para estudio de eficacia.

Estudio de eficacia: se cultivan explantes de cartílago durante 2-3 días en medio DMEM en un ambiente a 37 °C y 5% de CO_2 para equilibrar el tejido. Los explantes se pesan (~250mg) y colocan en pozos de un plato de cultivo de 24 pozos en 1 ml de medio y tres réplicas por grupo de tratamiento. Para el estudio de eficacia, los explantes de cartílago se cultivan durante seis días en la presencia o ausencia de varias concentraciones del compuesto de ensayo. El medio de reemplaza en el día 3 y el experimento se termina en el día 6. El contenido de agrecán total del medio condicionado se mide mediante un ensayo colorimétrico con DMMB (Farndale, RW et al., Biochim BiophysActa. 1986, 883, 173-177).

Estudio de metabolismo de agrecán en cartílago: el estudio del metabolismo en cartílago se desarrolla con el compuesto de ensayo 800. Los explantes de cartílago inmediatamente después de cosecha se cultivan en la presencia o ausencia del

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compuesto de ensayo 800. En el día 3, el medio se recolecta y se reemplaza con medio, compuesto de ensayo y sulfato etiquetado ($^{35}SO_4$, 5 mCi, Perkin Elmer, Boston, MA). En el día 6, se recolecta el medio, se lavan los explantes y se reemplazan con medio y compuesto de ensayo 800. En el día 9, el medio se recolecta, los explantes se lavan y el tejido restante se digiere con proteinasa K (Sigma). Las muestras se separan en columnas NAP10 (Pharmacia, Uppsala, Suiza) para separar la etiqueta libre y sintetizar nuevamente en agrecán etiquetado. Las moléculas de agrecán etiquetadas se cuentan utilizando opti-fluor (Perkin Elmer) y un instrumento de medición-centelleo líquido (Beckman Coulter, Fullerton, CA). Se estima el porcentaje del agrecán sintetizado nuevamente en cartílago y medio.

Análisis Western: Fragmentos de agrecán en medio condicionado se analizan por análisis western utilizando anticuerpo de neoepítopo, BC-3 diseñado para reconocer el neoepítopo interglobular de terminal N generado agrecanasa ^{374}ARGS. Medio condicionado de peso equivalente de cartílago de cada pozo de réplica por grupo de tratamiento se agrupa y digiere con ABC condroitinasa (Sigma, St Louis, MO), Keratinasa I (Seikagaku America, Falmouth, MA) y Keratinasa II (Seikagaku America, Falmouth, MA) durante 2 h a 37 °C. Las muestras se concentran mediante dispositivo de filtro centrífugo YM-10 (Millipore Corp., Bedford, MA), se liofilizan y reconstituyen con volumen igual de agua. Las muestras se separan bajo condiciones de reducción en 4-12% de gradiente de geles Tris-glicina (Invitrogen, Carlsbad, CA). Las proteínas de los

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geles se transfieren a membranas de nitrocelulosa. Los inmunoblots se sondean utilizando Mab BC-3 (Abeam, Cambridge, MA). Se desarrolla incubación con primario e IgG anti ratón de cabra secundario conjugado con alcalino-fosfatasa (Promega Corp., Madison, WI) se desarrolla durante la noche a 4 °C y a temperatura ambiente durante 1h, respectivamente. Los inmunoblots se incuban con sustrato NBT/BCIP (Promega Corp., Madison, WI) a temperatura ambiente para alcanzar un desarrollo óptimo de color. Los fragmentos de agrecán que contienen el neoepítopo ARGS se cuantifican por análisis de desitometría y se determina el porcentaje de inhibición de la degradación de agrecán por los compuestos de ensayo.

Resultados

Eficacia de los compuestos de ensayo 800, 8NNNNNNN, y 8WWWWWWW:

Información de donantes humanos que incluyen edad y sexo en la Tabla 4b, 5b, y 6b. Los cartílagos de todos los donantes se colocan en cultivo que exhibe segmentación de agrecán mediada por agrecanasa y cuando se tratan con los compuestos de ensayo muestran inhibición dependiente de la dosis de segmentación de agrecán mediado por agrecanasa. Los resultados de la inhibición de la actividad de agrecanasa en términos de inhibición de agrecanasa genera fragmentos de agregan mediante los compuestos de ensayo que se muestran en la Tabla 4a, 5a, y 6a. Basado en estos resultados, el EC_{50} del compuesto de ensayo 800 se determina por ser de

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aproximadamente 150 ng/ml (Figura 1), EC_{50} para el compuesto de ensayo 8WWWWWWW que se aproxima a 40-160 ng/ml; y EC_{50} para el compuesto de ensayo 8NNNNNNN que es menor de 40 ng/ml. Sin embargo, el compuesto de ensayo 8WWWWWWW y el compuesto de ensayo 8NNNNNNN se prueba solo en 8 a 4 donantes, respectivamente. El compuesto de ensayo 800 se prueba en un total de 15 donantes

Efecto del compuesto de ensayo 800 en metabolismo agrecán: se analiza cartílago articular de tres donantes OA humanos para el efecto del compuesto de ensayo 800 en el agrecán sinterizado nuevamente. El cartílago de todos los tres donantes muestra la capacidad de sintetizar nuevas moléculas de agrecán que está en la matriz del cartílago o liberado en el medio condicionado. El cartílago de todos los tres donantes se trata con el compuesto 80o que muestra incremento en la dependencia de dosis en el contenido de agrecán sintetizado nuevamente de la matriz de cartílago y una reducción equivalente en la liberación de agrecán en el medio (Figura 2).

La actividad de la agrecanasa es una característica de la osteoartritis humana a través del proceso de la enfermedad. El análisis del agrecán liberado del cartílago articular osteoartrítico humano revela degradación creciente significativa del agrecán por agrecanasas en donantes humanos probados. La inhibición de la actividad agrecanasa por los inhibidores selectivos de agrecanasa reduce la liberación de

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los productos de degradación del agrecán de la matriz de cartílago articular.

En razón a que el agrecán sintetizado nuevamente parece ser susceptible a la degradación por agrecanasas, la inhibición de agrecanasa selectiva resulta en un incremento neto en la incorporación de agrecán en la matriz de cartílago. Estos resultados indican que la inhibición de agrecanasas reducirá la degradación del agrecán en el cartílago articular osteoertrítico humano a través del proceso de la enfermedad, y también resulta en un incremento neto en el agrecán de matriz extracelular.

Tabla 4

A) Eficacia del compuesto de ensayo 800 en estudios de explantes humanos

Compuesto 800 (Análisis BC3)		
Conc. de Compuesto (ug/ml)	Promedio de 15 donantes	
	% de Inbición	SDM
0.02	8.52	
0.04	26.16	*5.33*
0.08	42.93	*7.86*
0.15	49.03	*7.87*
0.3	56.40	*5.95*
0.6	73.92	*5.24*
1.25	83.36	*5.59*
2.5	100.94	*4.12*
5	98.88	*1.32*
10	101.60	*0.99*
~EC50 = 150 ng/ml		

B) Información de donante humano para estudios 800 de compuesto de ensayo

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Compuesto 800(into donante)	
Sexo	Edad
F	65
M	83
M	70
F	56
F	76
M	53
F	77
F	74
F	75
M	79
M	61
F	57
M	72
M	70
M	62

Tabla 5

A) Eficacia del compuesto de ensayo 8WWWWWWW en estudios de explantes humanos

Compuesto8WWWWWWW (Análisis BC3)		
Conc. de Compuesto (ug/ml)	Promedio de 8 donantes	
	% de Inbición	SDM
0.01	2.85	*2.85*
0.02	46.39	*15.95*
0.04	23.50	*10.57*
0.08	76.91	*5.99*
0.15	88.47	*3.25*
0.3	95.03	*1.70*
0.6	98.03	*0.90*
1.25	100.30	*0.55*
-EC50 = 40-160 ng/ml		

B) Información de donante humano para estudios 8WWWWWWW de compuesto de ensayo

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Compuesto ensayo (Info donante)	
Sexo	Edad
F	69
F	69
F	63
M	60
M	57
F	72
F	65
F	75

Tabla 6

A) Eficacia del compuesto de ensayo 8NNNNNNN en estudios de explantes humanos

Compuesto ensayo 8NNNNNNN (Análisis BC3)		
Conc. de Compuesto (ug/ml)	Promedio de 4 donantes	
	% de Inbición	SDM
0.04	70.22	
0.08	84.46	
0.15	66.74	*10.97*
0.3	73.14	*19.73*
0.6	98.93	*0.92*
1.25	99.43	*1.44*
2.5	98.66	*2.20*
5	100.21	*1.15*
10	101.15	*0.42*
-EC50 =Menor de 40 ng/ml		

B) Información de donante humano para estudios 8NNNNNNN de compuesto de ensayo

Compuesto ensayo (Info donante)	
Sexo	Edad
M	63
F	68
F	72
F	60

Mientras que las modalidades particulares de la presente invención se han ilustrado y descrito, será obvio para aquellos expertos en la técnica que se pueden hacer otras modificaciones y varios cambios sin apartarse del espíritu y

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alcance de la invención. Esta por lo tanto está destinada a cubrir en las reivindicaciones adjuntas todos tales cambios y modificaciones que están dentro del alcance de esta invención.

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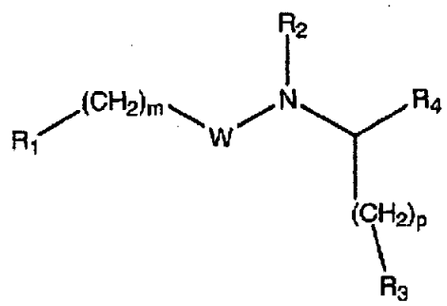
REIVINDICACIONES

Lo que se reivindica es:

1. Un compuesto de la Fórmula (I):



(I)

o una sal farmacéuticamente aceptable de este,

en donde

W es -C(O)-, -OC(O)-, -NHC(O)-, -C(O)O-, o -C(O)NH-;

R_1 es fenilo, heteroarilo, bifenilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada uno se sustituye opcionalmente con uno o más de R_5 o R_6, y cuando R_1 se sustituye con más de uno de R_5 o R_6, los sustituyentes pueden ser idénticos o diferentes;

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), $-(CH_2)_nR_{11}$, -OH, o -O-alquilo (C_1-C_6);

R_3 es $-CO_2H$, $-CONH_2$, -CONHOH, $-CONHSO_2R_7$, tetrazol, $-SO_2NHR_7$, $-SO_3H$, $-PO(OH)NH_2$, $-PO(OH)OR_7$, $-CONHR_7$, $-COOR_7$, un grupo de ácido mimético, o un heterocicloalquilo de 5 o 6

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miembros o heteroarilo que contiene 1 a 4 heteroátomos seleccionados de O, N, S;

R_4 es $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, o $-CONR_9R_{10}$;

R_5 es arilo, heteroarilo, $-(CH_2)_n$-arilo, $-(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, -S-heteroarilo, -NH-arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO-arilo, -CO-heteroarilo, $-SO_2$-alquilo (C_1-C_6), $-SO_2$-arilo, $-SO_2$-heteroarilo, $-SO_2NH$-arilo, $-SO_2NH$-heteroarilo, $-NHSO_2$-alquilo (C_1-C_6), $-NHSO_2$-arilo, $-NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R_5 se sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes;

R_6 y R_{12} son cada uno independientemente hidrógeno, halógeno, -CN, $-OCF_3$, $-CF_3$, $-NO_2$, -OH, -SH, $-NR_7R_8$, $-CONR_7R_8$, $-NR_8COR_7$, $-NR_8CO_2R_7$, $-CO_2R_7$, $-COR_7$, $-SO_2$-alquilo (C_1-C_6), $-SO_2$-arilo, $-SO_2$-heteroarilo, $-SO_2R_7$, $-NR_7SO_2R_8$, $-SO_2NR_7R_8$, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6),

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-NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, -$(CH_2)_n$-arilo, o -$(CH_2)_n$-heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_9 y R_{10} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), alquilo (C_1-C_6)-OH, alquilo (C_1-C_6)-O-alquilo (C_1-C_6), arilo, cicloalquilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más R_{12}; o R_9 y R_{10} juntos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

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R_{11} es arilo, heteroarilo, o cicloalquilo;

R_{13} es halógeno, -O-alquilo (C_1-C_6), $-CO_2H$, -OH, $-CF_3$, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con $-NH_2$, arilo sustituido con -O-alquilo (C_1-C_6), $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo;

m es 0-4;

n es 0-4; y

p es 0-2.

2. El compuesto o sal de la reivindicación 1, en donde W es -CO.

3. El compuesto o sal de la reivindicación 1 o reivindicación 2, en donde R_3 es $-CO_2H$.

4. El compuesto o sal de una cualquiera de las reivindicaciones 1 a 3, en donde R_1 es arilo bicíclico opcionalmente sustituido con uno o más de R_5 y R_6, en donde R_5 y R_6 se definen como en la reivindicación 1.

5. El compuesto o sal de una cualquiera de las reivindicaciones 1 a 3, en donde R_1 es arilo tricíclico opcionalmente sustituido con uno o más de R_5 y R_6, en donde R_5 y R_6 se definen como en la reivindicación 1.

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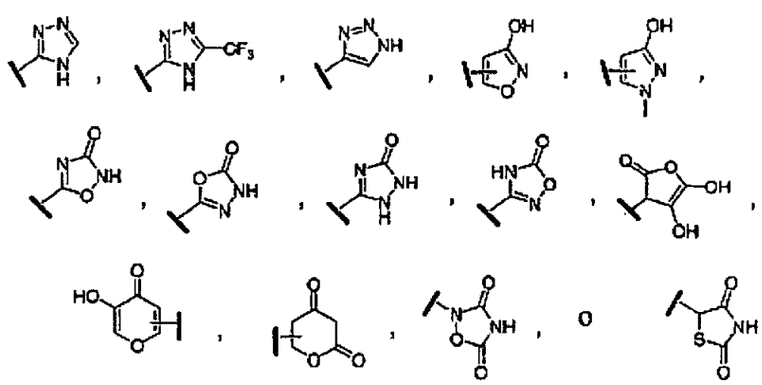
6. El compuesto o sal de una cualquiera de las reivindicaciones 1 a 3, en donde R_1 es bifenilo opcionalmente sustituido con uno o más de R_5 y R_6, en donde R_5 y R_6 se definen como en la reivindicación 1.

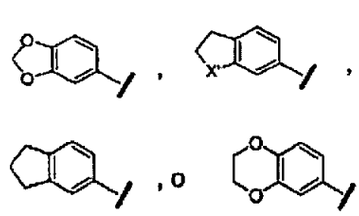
7. El compuesto o sal de una cualquiera de las reivindicaciones 1 a 6, en donde m es 0 y p es 2.

8. El compuesto o sal de una cualquiera de las reivindicaciones 1 a 7, en donde R_4 es $-CO_2H$, $-CONH_2$, $-(CH_2)_nOR_7$, o $-CONR_9R_{10}$, en donde R_7, R_9, R_{10}, y n se definen como en la reivindicación 1.

9. El compuesto o sal de una cualquiera de las reivindicaciones 1 a 8, en donde R_3 Es



10. El compuesto o sal de una cualquiera de las reivindicaciones 1 a 9, en donde R_5 es



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en donde X' es O, S, o NH.

11. El compuesto o sal de la reivindicación 1, en donde

W es -CO,

R_2 es hidrógeno,

R_3 es $-CO_2H$,

R_1 es bifenilo opcionalmente sustituido con uno o más de R_5 y R_6,

R_4 es $-CONR_9R_{10}$,

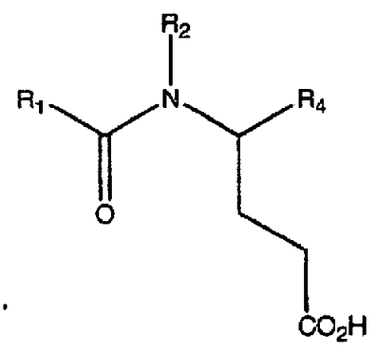
m es 0,

p es 2, y

R_5, R_6, R_9, y R_{10} se definen como en la reivindicación 1.

12. El compuesto o sal de una cualquiera de las reivindicaciones 1 a 11, en donde el compuesto o sal farmacéuticamente aceptable del compuesto es el S-enantiómero con respecto al carbono al cual R_4 se une.

13. El compuesto de la reivindicación 1 de la Fórmula (Ia):



(Ia)

o una sal farmacéuticamente aceptable de este,

en donde

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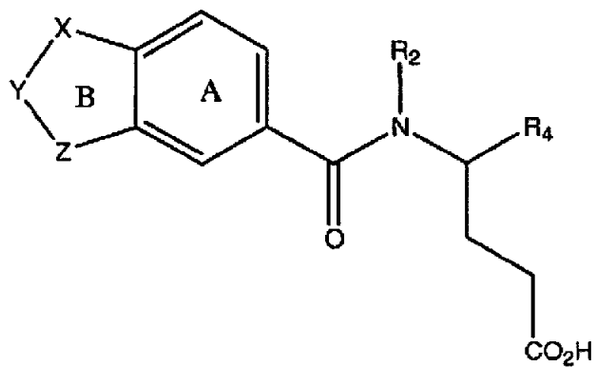
R_1, R_2, y R_4 son como se define en una cualquiera de las reivindicaciones 1, 3, 4, 5 o 8.

14. El compuesto de la reivindicación 1 de la Fórmula (Ib):



(Ib)

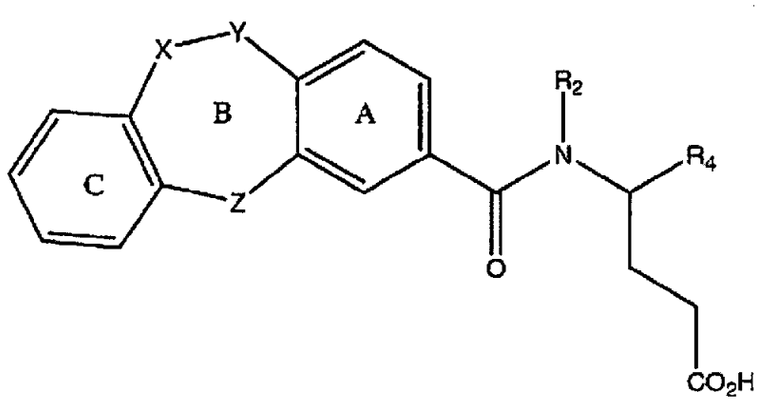
o una sal farmacéuticamente aceptable de este,

en donde

X, Y, y Z son cada uno independientemente $(CH_2)_n$, O, S, NR_7, CO, o SO_2; o X, Y, y Z forman un benceno en el anillo B; el anillo A y el anillo B son cada uno independientemente sustituidos opcionalmente con uno o más de R_5 y R_6; y

R_2, R_4, R_5, R_6, R_7, y n son como se define en una cualquiera de las reivindicaciones 1, 8 o 10.

15. El compuesto de la reivindicación 1 de la Fórmula (Ic):



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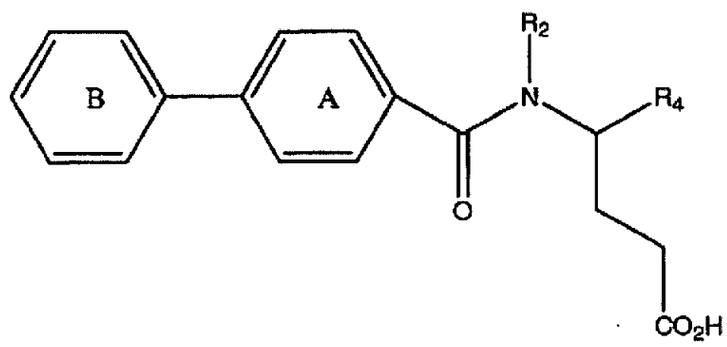
o una sal farmacéuticamente aceptable de este,

en donde

X, Y, y Z son cada uno independientemente $(CH_2)_n$, O, S, NR_7, CO, o SO_2; o X, Y, y Z forman un benceno en el anillo B; el anillo A, el anillo B, y el anillo C son cada uno independientemente sustituidos opcionalmente con uno o más de R_5 y R_6; y

R_2, R_4, R_5, R_6, R_7, y n son como se define en una cualquiera de las reivindicaciones 1, 8 o 10.

16. El compuesto de la reivindicación 1 de la Fórmula (Id):



(Id)

o una sal farmacéuticamente aceptable de este,

en donde

el anillo A y el anillo B son cada uno independientemente sustituidos opcionalmente con uno o más de R_5 y R_6; y

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R_2, R_4, R_5, y R_6 son como se define en una cualquiera de las reivindicaciones 1, 8 y 10.

17. El compuesto de la reivindicación 16 o una sal farmacéuticamente aceptable de este,

en donde

R_2 es hidrógeno,

R_4 es

, y

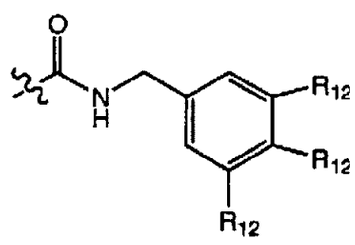
R_{12} es -F.

18. El compuesto de la reivindicación 15 o una sal farmacéuticamente aceptable de este,

en donde

cada uno de X, Y, y Z es independientemente $(CH_2)_n$, con n = 1 para uno de X, Y, y Z y n = 0 para el otro de X, Y, y Z; R_2 es hidrógeno;

R_4 es



, y

cada R_{12} es $-OCH_3$.

19. El compuesto de la reivindicación 15 o una sal farmacéuticamente aceptable de este,

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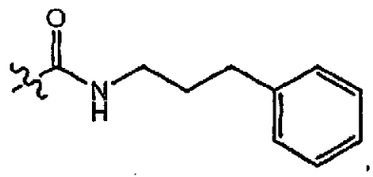
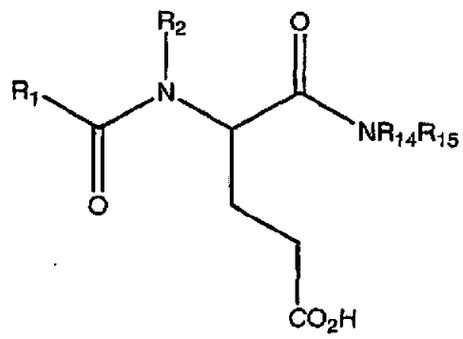
en donde cada uno de X, Y, y Z es independientemente $(CH_2)_n$, con n = 1 para uno de X, Y, y Z, y n = 0 para el otro de X, Y, y Z; R_2 es hidrógeno; y

R_4 es



20. Un compuesto de la Fórmula (II):



(II)

o una sal farmacéuticamente aceptable de este,

en donde

R_1 es fenilo, heteroarilo, bifenilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada uno se sustituye opcionalmente con uno o más de R_5 o R_6, y cuando R_1 se sustituye con más de uno de R_5 o R_6, los sustituyentes pueden ser idénticos o diferentes;

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), $-(CH_2)_pR_{11}$, -OH, o -O-alquilo (C_1-C_6);

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R_5 es arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, -S-heteroarilo, -NH-arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO-arilo, -CO-heteroarilo, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2NH-arilo, -SO_2NH-heteroarilo, -$NHSO_2$-alquilo (C_1-C_6), -$NHSO_2$-arilo, -$NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R_5 se sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes;

R_6 y R_{12} son cada uno independientemente hidrógeno, halógeno, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo,

$-(CH_2)_n$-arilo, $-(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_{11} es arilo, heteroarilo, o cicloalquilo;

R_{13} es halógeno, -O-alquilo (C_1-C_6), $-CO_2H$, -OH, $-CF_3$, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con $-NH_2$, arilo sustituido con -O- alquilo(C_1-C_6), $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo;

R_{14} y R_{15} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, heterocicloalquil-$(CH_2)_n$-arilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, o heteroarilo

se sustituye opcionalmente con uno o más R_{12}; o R_{14} y R_{15} junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

n es 0-4, y

p es 0-2.

21. El compuesto o sal farmacéuticamente aceptable del compuesto de la reivindicación 1, en donde el compuesto es

N^2-(4-benzoilbenzoil)-*N*^{1}-bencil-L-α-glutamina

ácido *N*-(4-benzoilbenzoil)-L-glutámico

N^1-(1,3-benzodioxol-5-ilmetil)-*N*^{2}-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-*N*^{1}-butil-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-*N*^{1}-ciclopropil-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-*N*^{1}-ciclohexil-L-α-glutamina

N^1-bencil-*N*^{2}-(4-tien-2-ilbenzoil)-L-α-glutamina

N^1-bencil-*N*^{2}-[4-(2-furil)benzoil]-L-α-glutamina

N^1-bencil-*N*^{2}-[(4'-etinil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-*N*^{1}-(4-fluorobencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-*N*^{1}-ciclooctil-L-α-glutamina

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N^1-bencil-N^2-(4-bromobenzoil)-L-α-glutamina

N^1-bencil-N^2-[(2',5'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-dimetoxibencil)-L-α-glutamina

N^1-bencil-N^2-(4-piridin-4-ilbenzoil)-L-α-glutamina

N^1-bencil-N^2-[(3'-5'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^1-bencil-N^2-[(4'-etil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^1-bencil-N^2-[(3'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^1-bencil-N^2-[(2'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^1-bencil-N^2-[(2',6'-dimetil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-ciclopentil-L-α-glutamina

N^1-[2-(acetilamino)etil]-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

N^1-2-adamantil-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

N^1-(2-adamantilmetil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

N^1-bencil-N^2-(4-piridin-2-ilbenzoil)-L-α-glutamina

N^1-bencil-N^2-(4-piridin-3-ilbenzoil)-L-α-glutamina

N^1-bencil-N^2-[4-(1,3-tiazol-2-il)benzoil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metoxibencil)-L-α-glutamina

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N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3,4-dimetoxifenil)etil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metoxietil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(4-metoxifenil)etil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(1-naftilmetil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-metilbencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-furilmetil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-metoxibencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,4-diclorobencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-(trifluorometoxi)bencil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[3-(trifluorometoxi)bencil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-(metiltio)bencil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fenoxibencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3-metoxifenil)etil]-L-α-glutamina

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N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,4-dimetoxibencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metoxibencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-diclorobencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,5-difluorobencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^5-hidroxi-N^1[3-(trifluorometoxi)bencil]-1-glutamamida

N^2-(1,1'-bifenil-4-ilcarbonil)-N^5-hidroxi-N^1-[2-(3-metoxifenil)etil]-1-glutamamida

N^2-(1,1'-bifenil-4-ilcarbonil)-N^5-hidroxi-N^1-(3,4,5-trimemoxibenzil)-L-glutamamida

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,5-dimetoxibencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,5- dimetoxibencil)-N^5-hidroxi-L-glutamamida

N^1-bencil-N^2-[(4'-vinil-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-dimetilbencil)-L-α-glutamina,

N^1-bencil-N^2-[(4'-etoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^1-bencil-N^2-[(4'-propoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^1-bencil-N^2-[(4'-butoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

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N^1-bencil-N^2-{[4'-(ciclobutilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina

N^1-bencil-N^2-{[4'-(ciclohexilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina

N^2-{[4'-(aliloxi)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N1-(3,4-dimetilbencil)-N^5-hidroxi-L-glutamamida

N^2-(1,1'-bifenil-4-ilacetil)-N^1-(3-metoxibencil)-L-α-glutamina

N^2-[(3-fluorofenil)acetill-N^1-(3-metoxibencil)-L-α-glutamina

N^2-{[4'-(acetilamino)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutamina

N^1-bencil-N^2-{[4'-(2-furoilamino)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina

N^1-bencil-N^2-({4'-[(4-fluorobenzoil)amino]-1,1'-bifenil-4-il}carbonil)-L-α-glutamina

N^2-{[4'-(benzoilamino)-1,1'-bifenil-4-il]carbonil}-N^1-bencil-L-α-glutamina

N^1-bencil-N^2-(5-fenil-2-furoil)-L-α-glutamina

N^1-bencil-N^2-[5-(3,5-etoxifenil)-2-furoil]-L-α-glutamina

N^1-bencil-N^2-[5-(3,5-dimetilfenil)-2-furoil]-L-α-glutamina

N^1-bencil-N^2-(2,2'-bifuran-5-ilcarbonil)-L-α-glutamina

N^1-bencil-N^2-(5-tien-2-il-2-furoil)-L-α-glutamina

N^2-[(2,2'-dimetil-1,1'-bifenil-4-il)carbonil]-N^1-(3-metoxibencil)-L-α-glutamina

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N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-feniletil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[3-(trifluorometil)bencil]-L-α-glutamina

N^1-(4-aminobencil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

N^1-(3-aminobencil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(trifluorometil)bencil]-L-α-glutamina

N^1-bencil-N^2-[(2-fluoro-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^2-(-1,1'-bifenil-4-ilcarbonil)-N^1-(3-fluorobencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutamina

N^1-bencil-N^2-(1,1'-bifenil-3-ilcarbonil)-L-α-glutamina

N^1-bencil-N^2-(3-tien-2-ilbenzoil)-L-α-glutamina

N^1-bencil-N^2-[(3-cloro1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^1-bencil-N^2-[(3-fluoro-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^1-bencil-N^2-[(2,6-dimetoxi-1,1'-bifenil-4-il)carbonil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(3-clorofenil)etil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-fluorobencil)-L-α-glutamina

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N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3,4-difluorobencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2-metilbencil)-L-α-glutamina

N^1-bencil-N^2-({4'-[(3-metoxibencil)oxi]-1,1'-bifenil-4-il}carbonil)-L-α-glutamina

N^1-bencil-N^2-({4'-[(3,5-dimetoxibencil)oxi]-1,1'-bifenil-4-il}carbonil)-L-α-glutamina

N^1-bencil-N^2-{[4'-(2-naftilmetoxi)-1,1'-bifenil-4-il]carbonil}-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-2,3-dihidro-1*H*-inden-2-il-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(2,3-dimetilbencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-fenilbutil)-L-α-glutamina

N^1-(2-bencilfenil)-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metoxi-1,1'-bifenil-3-il)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-metilbencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[4-fluoro-3-(trifluorometil)bencil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-heptil-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-yodobencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-vinilbencil)-L-α-glutamina

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N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(3-tien-2-ilbencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina,

N^1-bencil-N^2-[(6-fenilpiridin-3-il)carbonill-L-α-glutamina

N^1-(3-metoxibencil)-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-*terc*-butilbencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-yodobencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-vinilbencil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(sec-butil)-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(ciclopropilmetil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[4-(dimetilamino)bencil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-bromofenil)etil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(2-bifenil-4-iletil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2'-etoxibifenil-4-il)etil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-etinilbifenil-4-il)etil]-L-α-glutamina

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N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4-(2-tienil)fenil]etil}-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-piridin-2-ilfenil)etil]-L-α-glutamina

N^2-bifenil-4-ilcarbonil)-N^1-[3-(dimetilamino)bencil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(3,3-difenilpropil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(3,3-dimetilbutil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-isopropil-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(piridin-4-ilmetil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1,N^1-dietil-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(1,1-dimetilpropil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-4-il)etil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4'-(trifluorometil)bifenil-4-il]etil}-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-formilbifenil-3-il)etil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-{2-[4'-(trifluorometil)bifenil-3-il]etil}-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-metoxibifenil-3-il)etil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4'-metoxibifenil-4-il)etil]-L-α-glutamina

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N^2-(bifenil-4-ilcarbonil)-N^1-[2-(3-bromofenil)etil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-pentil-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-piridin-4-ilfenil)etil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(*terc*-butil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-{[4'-(trifluorometil)bifenil-3-il]metil}-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(2,2-dimetilpropil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[(4'-etinilbifenil-3-il)metil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(3-piridin-2-ilbencil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(1,1-dimetil-2-feniletil)-L-α-glutamina,

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-hexil-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(1-metil-1-feniletil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(1,1,3,3-tetrametilbutil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(2-morfolin-4-iletil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(2-hidroxi-1,1-dimetiletil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)etil]-L-α-glutamina

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N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-fluorofenil)etil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-clorofenil)etil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-tienil)etil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(2-clorofenil)etil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-(5-hidroxipentyl)-L-α-glutamina

ácido 3-[(bifenil-4-ilmetil)amino]-3-oxopropanóico

N^2-(bifenil-4-ilcarbonil)-N^1-propil-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-D-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(3-piridin-2-ilfenil)etil]-L-α-glutamina

N^2-2-naftoil-N^1-(3-fenilpropil)-L-α-glutamina

N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutamina

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N^2-(9*H*-fluoren-1-ilcarbonil)-N^1-(3-fenilpropil)-L-α-glutamina

N^2-(4-fenoxibenzoil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-(9*H*-fluoren-2-ilcarbonil)-N^1-hexil-L-α-glutamina

N^2-(9*H*-fluoren-1-ilcarbonil)-N^1- hexil-L-α-glutamina

N^1-hexil-N^2-(4-fenoxibenzoil)-L-α-glutamina

N^1-hexil-N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-L-α-glutamina

N^2-[(9-oxo-9*H*-fluoren-2-il)carbonil]-N^1-(3-fenilpropil)-L-α-glutamina

N^2-(4-fenoxibenzoil)-N^1-(3-fenilpropil)-L-α-glutamina

ácido *N*-[4-(pirimidin-2-ilamino)benzoil]-1-glutámico

ácido *N*-(1,1'-bifenil-4-ilcarbonil)-D-glutámico

N-[4-(pirimidin-2-ilamino)benzoil]-L-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-D-α-glutamina

N^2-(1,1'-bifenil-4-ilcarbonil)-N^1-(4-hidroxibutil)-L-α-glutamina

N^1-bencil-N^2-(1,1'-bifenil-4-ilcarbonil)-L-α-glutamina

N^1-bencil-N^2-[4-(pirimidin-2-ilamino)benzoil]-L-α-glutamina

ácido (4S)-4-[(1,1'-bifenil-4-ilcarbonil)amino]-5-hidroxipentanóico

ácido *N*-({4'-[(fenilacetil)amino]-1,1'-bifenil-4-il}carbonil)-1-glutámico

ácido *N*-[(4'-{[(3-metil-1-benzofurano-2-il)carbonil]amino}-1,1'-bifenil-4-il)carbonil]-1-glutámico

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ácido *N*-{[4'-(2-furoilamino)-1,1'-bifenil-4-il]carbonil}-1-glutámico

ácido *N*-{[4'-(acetilamino)-1,1'-bifenil-4-il]carbonil}-L-glutámico

ácido *N*-{[4'-(benzoilamino)-1,1'-bifenil-4-il]carbonil}-1-glutámico

ácido *N*-({4'-[(1-benzofurano-2-ilcarbonil)amino]-1,1'-bifenil-4-il}carbonil)-1-glutámico

N^1-(1,1-dimetil-2-feniletil)-N^2-(9H-fluoren-2-ilcarbonil)-L-α-glutamina

N^1-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-(9*H*-fluoren-2-ilcarbonil)-L-α-glutamina

N^2-(9H-fluoren-2-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutamina

N^1-(6-hidroxihexil)-N^2-(4-fenoxibenzoil)-L-α-glutamina

N^2-(9H-fluoren-9-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutanúne

N^2-(9H-fluoren-9-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-(3-fenoxibenzoil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-(9H-fluoren-4-ilcarbonil)-N^1-(3,4,5-trimetoxibencil)-L-α-glutamina

N^1-1-adamantil-N^2-[(9-oxo-9H-fluoren-2-il)carbonil]-L-α-glutamina

N^1-1-adamantil-N^2-(4-fenoxibenzoil)-L-α-glutamina

N^1-1-adamantil-N^2-(9H-fluoren-2-ilcarbonil)-L-α-glutamina

N^1-1-adamantil-N^2-(9H-fluoren-9-ilcarbonil)-L-α-glutamina

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N^2-(9H-fluoren-2-ilcarbonil)-N^1-(3-metilbencil)-L-α-glutamina

N^1-(3-metilbencil)-N^2-[(9-oxo-9H-fluoren-2-il)carbonil]-L-α-glutamina

N^2-(9H-fluoren-9-ilcarbonil)-N^1-(3-metilbencil)-L-α-glutamina

N^2-(9H-fluoren-2-ilcarbonil)-N^1-propil-L-α-glutamina

N^1-bencil-N^2-[(9-oxo-9H-fluoren-2-il)carbonil]-L-α-glutamina

N^1-bencil-N^2-(9H-fluoren-2-ilcarbonil)-L-α-glutamina

N^1-bencil-N^2-(9H-fluoren-9-ilcarbonil)-L-α-glutamina

N^1-bencil-N^2-(3-fenoxibenzoil)-L-α-glutamina

N^1-(1-metil-1-feniletil)-N^2-[(9-oxo-9H-fluoren-2-il)carbonil]-L-α-glutamina

N^2-(9H-fluoren-9-ilcarbonil)-N^1-(1-metil-1-feniletil)-L-α-glutamina

N^1-(1-metil-1-feniletil)-N^2-(3-fenoxibenzoil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[(1S)-1-feniletil]-L-α-glutamina

N^2-(9H-fluoren-2-ilcarbonil)-N^1-[(1S)-1-feniletil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[(1S)-1-(4-fluorofenil)etil]-L-α-glutamina

terc-butil N^2-(bifenil-4-ilcarbonil)-N^1-(1-feniletil)-L-α-glutaminato

N^2-(bifenil-4-ilcarbonil)-N^1-[(1R)-1-(4-fluorofenil)etil]-L-α-glutamina

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N^2-(bifenil-4-ilcarbonil)-N^1-[(1R)-1-feniletil]-L-α-glutamina

N^2-(9H-fluoren-2-ilcarbonil)-N^1-[(1R)-1-feniletil]-L-α-glutamina

N^2-(9H-fluoren-1-ilcarbonil)-N^1-(6-hidroxihexil)-L-α-glutamina

N^1-(6-hidroxihexil)-N^2-[(9-oxo-9H-fluoren-2-il)carbonil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-9H-fluoren-9-il-L-α-glutamina

N^2-(9H-fluoren-2-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-[(3'-etoxibifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-[(2'-etoxibifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-[(4'-metoxibifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-(4-bromobenzoil)-N-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-[(3'-metoxibifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina

ácido 4'-{[((1S)-3-carboxi-1-{[(3,4,5-trimetoxibencil)amino]carbonil}propil)amino]carbonil}bifenil-3-carboxílico

N^2-[(4'-etilbifenil-4-il)carbonil]-N-(3,4,5-trimetoxibencil)-L-α-glutamina

N-bencil-N^2-[4-(2-naftil)benzoil]-L-α-glutamina

N^2-[(3',4'-dimetoxibifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-[(2',4'-dimetoxibifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N-(3,4,5-trimetoxibencil)-N^2-[(3',4',5'-trimetoxibifenil-4-il)carbonil]-L-α-glutamina

N-(1-adamantilmetil)-N^2-(bifenil-4-ilcarbonil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(3'-metoxibifenil-4-il)carbonil]-L-α-glutamina

N^2-[(3',4'-dimetoxibifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(2'-etoxibifenil-4-il)carbonil]-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(3'-fluoro-4'-metilbifenil-4-il)carbonil]-L-α-glutamina

N^2-(4-bromobenzoil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N-[(1S)-1-bencil-2-hidroxietil]-N^2-(bifenil-4-ilcarbonil)-L-α-glutamina

N-[(1S)-1-bencil-2-hidroxietil]-N^2-(9H-fluoren-2-ilcarbonil)-L-α-glutamina

N-(1-adamantilmetil)-N^2-(4-bromobenzoil)-L-α-glutamina

N-(1-adamantilmetil)-N^2-[(4'-hidroxibifenil-4-il)carbonil]-L-α-glutamina

N^2-[4-(1,3-benzodioxol-5-il)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N^2-[(2',4'-dimetoxibifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

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N^2-[(3'-fluoro-4'-metilbifenil-4-il)carbonil]-*N*-(3,4,5-txymetoxibencil)-L-α-glutamina

N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N-(1-adamantilmetil)-N^2-({4'-[(3-metoxibencil)oxi]bifenil-4-il}carbonil)-L-α-glutamina

N-(1-adamantilmetil)-N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-*N*-metil-*N*-(2-feniletil)-L-α-glutamina

N^2-[(4'-sec-butilbifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(4'-isopropilbifenil-4-il)carbonil]-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-(1,1':4',1''-terfenil-4-ilcarbonil)-L-α-glutamina

N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N^2-[(4'-hidroxibifenil-4-il)carbonil]-*N*-(3,4,5-txymetoxibencil)-L-α-glutamina

N-(1-adamantilmetil)-N^2-({3'-[(dimetilamino)carbonil]bifenil-4-il}carbonil)-L-α-glutamina

N-(1-adamantilmetil)-N^2-[(3',5'-dimetilbifenil-4-il)carbonil]-L-α-glutamina

N^2-(9H-fluoren-2-ilcarbonil)-*N*-metil-*N*-(2-feniletil)-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(3'-metilbifenil-4-il)carbonil]-L-α-glutamina

N^2-({4'-[(3,5-dimetilbencil)oxi]bifenil-4-il}carbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-[(4'-{[3,5-bis(trifluorometil)bencil]oxi}bifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-[(3'-isopropilbifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-[(4'-isopropilbifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N-(1-adamantilmetil)-N^2-[4-(1-benzofurano-5-il)benzoil]-L-α-glutamina

N-(1-adamantilmetil)-N^2-[4-(1H-indol-5-il)benzoil]-L-α-glutamina

N^2-[(3'-etoxibifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(3'-metoxibifenil-4-il)carbonil]-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(3'-isopropilbifenil-4-il)carbonil]-L-α-glutamina

N^2-[(3'-fluoro-4'-metilbifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(4'-isobutilbifenil-4-il)carbonil]-L-α-glutamina

N^2-(1,1':4'1''-terfenil-4-ilcarbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N-bencil-N^2-{[3'-(hidroximetil)bifenil-4-il]carbonil}-L-α-glutamina

N-bencil-N^2-({4'-[(3-fluorobencil)oxi]bifenil-4-il}carbonil)-L-α-glutamina

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N-bencil-N^2-{[4'-(benciloxi)bifenil-4-il]carbonil}-L-α-glutamina

N-bencil-N^2-[4-(feniletinil)benzoil]-L-α-glutamina

N-bencil-N^2-{4-[(9-hidroxi-9H-fluoren-9-il)etinil]benzoil}-L-α-glutamina

N-bencil-N^2-{4-[(1E)-3-oxo-3-fenilprop-1-en-1-il]benzoil}-L-α-glutamina

N-(3,4,5-trimetoxibencil)-N^2-[(2',4',6'-trimetilbifenil-4-il)carbonil]-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-({4'-[(3-metoxibencil)oxi]bifenil-4-il}carbonil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(4'-hidroxibifenil-4-il)carbonil]-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(3'-etoxibifenil-4-il)carbonil]-L-α-glutamina

N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-*N*-(6-hidroxihexil)-L-α-glutamina

N^2-({4'-[(3-metoxibencil)oxi]bifenil-4-il}carbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-(4-bromobenzoil)-*N*-(3-metilbencil)-L-α-glutamina

N^2-[4-(1,3-benzodioxol-5-il)benzoil]-*N*-(3-metilbencil)-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-*N*-butil-*N*-metil-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(4'-hidroxibifenil-4-il)carbonil]-L-α-glutamina

N-butil-N^2-(9H-fluoren-2-ilcarbonil)-*N*-metil-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-*N*-[2-(3,4-dimetoxifenil)etil]-*N*-metil-L-α-glutamina

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N^2-[4-(1,3-benzodioxol-5-il)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N-[2-(3,4-dimetoxifenil)etil]-N^2-(9H-fluoren-2-ilcarbonil)-*N*-metil-L-α-glutamina

N^2-(9H-fluoren-2-ilcarbonil)-*N*-[(2R)-2-fenilpropil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-*N*-[(2R)-2-fenilpropil]-L-α-glutamina

N-bencil-N^2-{4-[(4-hidroxiciclohexil)etinil]benzoil}-L-α-glutamina

N^2-{4-[(3-aminofenil)etinil]benzoil}-*N*-bencil-L-α-glutamina

N-bencil-N^2-[4-(3-hidroxi-3,3-difenilprop-1-in-1-il)benzoil]-L-α-glutamina

N-bencil-N^2-{4-[(3-metoxifenil)etinil]benzoil}-L-α-glutamina

N^2-[(3'-hidroxibifenil-4-il)carbonil]-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-{[4'-(hidroximetil)bifenil-4-il]carbonil}-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(4'-metilbifenil-4-il)carbonil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-N^1-[2-(4-fluorofenil)-1,1-dimetiletil]-L-glutamamida

N^2-({4'-[(3-terc-butilfenoxi)metil]bifenil-4-il}carbonil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N^2-({4'-[(3,5-di-terc-butilfenoxi)metil]bifenil-4-il}carbonil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

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N-(1,1-dimetil-2-feniletil)-N^2-({4'-[(3-etilfenoxi)metil]bifenil-4-il}carbonil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-({4'-[(3-metoxifenoxi)metil]bifenil-4-il}carbonil)-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(3'-hidroxibifenil-4-il)carbonil]-L-α-glutamina

N^2-(bifenil-4ilcarbonil)-N^1-[2-(4-fluoropenil)-1,2-dimetiletil]-N^5-hidroxi-L-glutamanida

N^2-[4-(5-bromo-2-tienil)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N-[2-(5-cloro-2-tienil)-1,1-dimetiletil]-N^2-[(3'-fluorobifenil-4-il)carbonil]-L-α-glutamina

N^2-[(3',4'-difluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(3',4'-difluorobifenil-4-il)carbonil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(2',4'-difluorobifenil-4-il)carbonil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(2',5'-difluorobifenil-4-il)carbonil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(2',6'-difluorobifenil-4-il)carbonil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(3',5'-difluorobifenil-4-il)carbonil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(2',3'-difluorobifenil-4-il)carbonil]-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-(4-pirimidin-5-ilbenzoil)-L-α-glutamina

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N^2-[(3',4'-difluorobifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N^2-[(3',5'-difluorobifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N-[2-(5-cloro-2-tienil)-1,1-dimetiletil]-N^2-[(3',4'-difluorobifenil-4-il)carbonil]-L-α-glutamina

N^2-(bifenil-4-ilcarbonil)-*N*-[2-(5-cloro-2-tienil)-1,1-dimetiletil]-L-α-glutamina

N^2-{[5-(3-cloro-4-fluorofenil)-2-tienil]carbonil}-*N*-[2-(5-cloro-2-tienil)-1,1-dimetiletil]-L-α-glutamina

N^2-{[4'-(hidroximetil)bifenil-4-il]carbonil}-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-{[4'-(bromometil)bifenil-4-il]carbonil}-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[4-(2-tienil)benzoil]-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[4-(2-furil)benzoil]-L-α-glutamina

N^2-{[4'-(hidroximetil)bifenil-4-il]carbonil}-*N*-(3-metilbencil)-L-α-glutamina

N^2-{[3'-(hidroximetil)bifenil-4-il]carbonil}-*N*-(3-metilbencil)-L-α-glutamina

N^2-[4-(2,3-dihidro-1-benzofurano-5-il)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-[(3'-cloro-4'-fluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-{[3'-(bromometil)bifenil-4-il]carbonil}-*N*-(3-metilbencil)-L-α-glutamina

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N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[4-(3-tienil)benzoil]-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[4-(5-metil-2-tienil)benzoil]-L-α-glutamina

N^2-[4-(5-cloro-2-tienil)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(2-tienil)benzoil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-{[5-(3-metoxifenil)-2-tienil]carbonil}-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(5-fenil-2-tienil)carbonil]-L-α-glutamina

N^2-(2,2'-bitien-5-ilcarbonil)-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-[4-(2,3-dihidro-1-benzofuran-6-il)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-{[6-(3-metoxifenil)piridin-3-il]carbonil}-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(5-fenil-2-tienil)carbonil]-L-α-glutamina

N^2-[(3-fluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(5-piridin-4-il-2-tnienil)carbonil]-L-α-glutamina

N^2-{[5-(3-cloro-4-fluorofenil)-2-tienil]carbonil}-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

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N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(2,3-dihidro-1-benzofurano-6-il)benzoil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(5-piridin-3-il-2-tienil)carbonil]-L-α-glutamina

N^2-[4-(2,3-dihidro-1-benzofurano-6-il)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N^2-{[5-(3-cloro-4-fluorofenil)-2-tienil]carbonil}-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[4-(2-tienil)benzoil]-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-{[5-(3-metoxifenil)-2-tienil]carbonil}-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(5-fenil-2-tienil)carbonil]-L-α-glutamina

N^2-(2,2'-bitien-5-ilcarbonil)-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(5-piridin-4-il-2-tienil)carbonil]-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(5-piridin-3-il-2-tienil)carbonil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(5-cloro-2-tienil)benzoil]-L-α-glutamina

N^2-{[6-(5-cloro-2-tienil)piridin-3-il]carbonil}-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-(5-fenil-2-furoil)-L-α-glutamina

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N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-{[6-(5-cloro-2-tienil)piridin-3-il]carbonil}-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(6-fenilpiridin-3-il)carbonil]-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-{[5-(3-metoxifenil)-2-tienil] carbonil}-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-[(5-piridin-3-il-2-tienil)carbonil]-L-α-glutamina

N^2-{[5-(3-cloro-4-fluorofenil)-2-tienil]carbonil}-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-(2,2'-bitien-5-ilcarbonil)-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(5-formil-2-tienil)benzoil]-L-α-glutamina

N^2-[4-(5-acetil-2-tienil)benzoil]-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[4-(1,3-tiazol-2-il)benzoil]-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[4-(1,3-tiazol-2-il)benzoil]-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-(5-fenil-2-furoil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[4-(5-formil-2-tienil)benzoil]-L-α-glutamina

N^2-[4-(5-acetil-2-tienil)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[3-(5-cloro-2-tienil)benzoil]-L-α-glutamina

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N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[3-(2-tienil)benzoil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-{[5-(4-clorofenil)-2-tienil]carbonil}-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-{[5-(4-fluorofenil)-2-tienil]carbonil}-L-α-glutamina

N^2-[4-(5-bromo-2-tienil)benzoil]-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-[4-(5-bromo-2-tienil)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-{[5-(4-fluorofenil)-2-tienil]carbonil}-L-α-glutamina

N^2-[3-(5-cloro-2-tienil)benzoil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[3-(2-tienil)benzoil]-L-α-glutamina

N^2-[(3'-clorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-[(4'-clorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-[(4'-fluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-[(3'-fluorobifenil-4-il)carbonil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N-[2-(4-clorofenil)-1,1-dimetiletil]-N^2-[(3-fenil-2-tienil)carbonil]-L-α-glutamina

N^2-[(4'-clorobifenil-4-il)carbonil]-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

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N^2-[(3'-clorobifenil-4-il)carbonil]-*N*-[2-(4-clorofenil)-1,1-dimetiletil]-L-α-glutamina

N-[2-(4-fluorofenil)-1,1-dimetiletil]-N^2-{[5-(4-fluorofenil)-2-tienil]carbonil}-L-α-glutamina

N^2-{[5-(4-clorofenil)-2-tienil]carbonil}-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(3-fenil-2-tienil)carbonil]-L-α-glutamina

N^2-(4-bromobenzoil)-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(4'-fluorobifenil-4-il)carbonil]-L-α-glutamina

N-(1,1-dimetil-2-feniletil)-N^2-[(3'-fluorobifenil-4-il)carbonil]-L-α-glutamina

N^2-[4-(5-cloro-2-tienil)benzoil]-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-D-α-glutamina

N^2-{[6-(5-cloro-2-tienil)piridin-3-il]carbonil}-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-{[5-(4-clorofenil)-2-tienil]carbonil}-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-{[5-(3,4-difluorofenil)-2-tienil]carbonil}-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N^2-[(4'-{[3,5-bis(trifluorometil)fenoxi]metil}bifenil-4-il)carbonil]-*N*-(1,1-dimetil-2-feniletil)-L-α-glutamina

N^2-({4'-[(1,3-benzodioxol-5-iloxi)metil]bifenil-4-il)carbonil)-*N*-(1,1-dimetil-1-feniletil)-L-α-glutamina

N^2-{[3'-(benciloxi)bifenil-4-il]carbonil}-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

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N^2-({3'-[(3-metoxibencil)oxi]bifenil-4-il}carbonil)-*N*-(3,4,5-trimetoxibencil)-L-α-glutamina

N^2-({4'-[(3,5-dimetoxibencil)oxi]bifenil-4-il}carbonil)-*N*-[2-(4-fluorofenil)-1,1-dimetiletil]-L-α-glutamina

N-bencil-N^2-{[4'-(bifenil-3-ilmetoxi)bifenil-4-il]carbonil}-L-α-glutamina

N-bencil-N^2-({4'-[(3'-metoxibifenil-3-il)metoxi]bifenil-4-il}carbonil)-L-α-glutamina

N^2-({4'-[(3,5-dimetoxifenoxi)metil]bifenil-4-il}carbonil)-*N*-(3-metilbencil)-L-α-glutamina

N^2-({3'-[(3,5-dimetoxifenoxi)metil]bifenil-4-il}carbonil)-*N*-(3-metilbencil)-L-α-glutamina

N^2-[(3'-{[3,5-bis(trifluorometil)fenoxi]metil}bifenil-4-il)carbonil]-*N*-(3-metilbencil)-L-α-glutamina

N^2-({3'-[(3-etilfenoxi)metil]bifenil-4-il}carbonil)-*N*-(3-metilbencil)-L-α-glutamina

N-bencil-N^2-{[4'-(bifenil-2-ilmetoxi)bifenil-4-il]carbonil}-L-α-glutamina

o

N-bencil-N^2-({4'-[(3'-metoxibifenil-2-il)metoxi]bifenil-4-il}carbonil)-L-α-glutamina.

22. Un método para modular la actividad de una metaloproitenasa en un animal en necesidad de este comprende poner en contacto la metaloproteinasa con una cantidad efectiva de un compuesto o sal reivindicada en una cualquiera de las reivindicaciones 1 a 21.

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23. El método de la reivindicación 22, en donde la metaloproteinasa es una metaloproteinasa matriz o una agrecanasa.

24. El método de la reivindicación 23, en donde la agrecanasa es agrecanasa-1 o agrecanasa-2.

25. Una composición que comprende una cantidad efectiva del compuesto o una sal farmacéuticamente aceptable del compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 21 y un portador farmacéuticamente aceptable.

26. La composición de la reivindicación 25, en donde el portador farmacéuticamente aceptable es adecuado para administración oral y la composición comprende una forma de dosificación oral.

27. Un método para tratar un trastorno relacionado con metaloproteinasa, en un animal en necesidad de este, que comprende, administrar una dosis efectiva del compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 21, o una sal farmacéuticamente aceptable o hidrato de este.

28. El método de la reivindicación 27, en donde la metaloproteinasa es una metaloproteinasa matriz o una agrecanasa.

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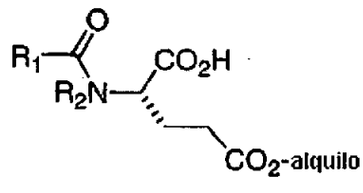
29. El método de la reivindicación 28, en donde la agrecanasa es agrecanasa-1 o agrecanasa-2.

30. El método de la reivindicación 27, en donde el trastorno relacionado con metaloproteinasa se selecciona del grupo que consiste de trastornos artríticos, osteoartritis, cáncer, artritis reumatoide, asma, enfermedad pulmonar obstructiva crónica, aterosclerosis, degeneración macular relacionada con la edad, infarto de miocardio, ulceración de córnea y otras enfermedades de superficie ocular, hepatitis, aneurismas aórticos, tendonitis, enfermedades del sistema nervioso central, cicatrización de heridas anormal, angiogénesis, reestenosis, cirrosis, esclerosis múltiple, glomerulonefritis, enfermedad del anfitrión versus el injerto, diabetes, enfermedad inflamatoria del intestino, choque, degeneración de disco intervertebral, apoplejía, osteopenia, y enfermedades periodontales.

31. El método de la reivindicación 30, en donde el trastorno relacionado con metaloproteinasa es osteoartritis.

32. Un método para sintetizar un compuesto que comprende:

a) tratar un compuesto de la Fórmula (III):



en donde

R_1 es fenilo, heteroarilo, bifenilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada uno se sustituye opcionalmente con uno o más de R_5 o R_6, y cuando R_1 se sustituye con más de uno de R_5 o R_6, los sustituyentes pueden ser idénticos o diferentes;

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), -$(CH_2)_nR_{11}$, -OH, o -O-alquilo (C_1-C_6);

R_5 es arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, -S-heteroarilo, -NH-arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO- arilo, -CO-heteroarilo, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2NH-arilo, -SO_2NH-heteroarilo, -$NHSO_2$-alquilo (C_1-C_6), -$NHSO_2$-arilo, -$NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH- alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R_5 se

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sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes;

R_6 es hidrógeno, halógeno, -CN, $-OCF_3$, $-CF_3$, $-NO_2$, -OH, -SH, $-NR_7R_8$, $-CONR_7R_8$, $-NR_8COR_7$, $-NR_8CO_2R_{75}$ $-CO_2R_7$, $-COR_7$, $-SO_2$-alquilo (C_1-C_6), $-SO_2$-arilo, $-SO_2$-heteroarilo, $-SO_2R_7$, $-NR_7SO_2R_8$, $-SO_2NR_7R_8$; alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo, $-(CH_2)_n$-arilo, $-(CH_2)_n$-heteroarilo, -O- arilo, -O-heteroarilo, -S-arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_{11} es arilo, heteroarilo, o cicloalquilo;

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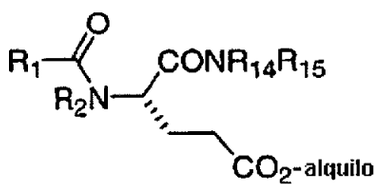
R_{13} es halógeno, -O-alquilo (C_1-C_6), $-CO_2H$, -OH, $-CF_3$, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con $-NH_2$, arilo sustituido con -O-alquilo (C_1-C_6), $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo; y

n es 0-4;

Con una amina, bajo condiciones efectivas para proporcionar un compuesto que tiene la fórmula (IV):



(IV);

en donde

R_{14} y R_{15} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, heterocicloalquil $-(CH_2)_n$- arilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más R_{12}; o R_{14} y R_{15} juntos pueden formar un grupo cíclico de cinco- a siete-miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S; y

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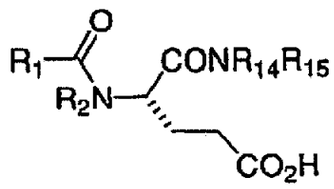
R_{12} es hidrógeno, halógeno, -CN, $-OCF_3$, $-CF_3$, $-NO_2$, -OH, -SH, $-NR_7R_8$, $-CONR_7R_8$, $-NR_8COR_7$, $-NR_8CO_2R_7$, $-CO_2R_7$, $-COR_7$, $-SO_2$-alquilo (C_1-C_6), $-SO_2$-arilo, $-SO_2$-heteroarilo, $-SO_2R_7$, $-NR_7SO_2R_8$, $-SO_2NR_7R_8$; alquilo (C_1-C_6) lineal, ramificado o cíclico, -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), o -NH-alquilo (C_1-C_6); heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6) cicloalquilo, -O-alquenilo, -O-alquil arilo (C_1-C_6), arilo, heteroarilo, $-(CH_2)_n$-arilo, $-(CH_2)_n$-heteroarilo, -O-arilo, -O- heteroarilo, -S-arilo, o -S-heteroarilo, cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13}; y

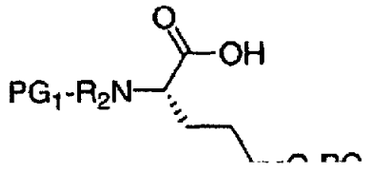
b) tratar el compuesto de la Fórmula (IV) bajo condiciones efectivas para la hidrólisis del éster de alquilo, suministrando por lo tanto un compuesto que tiene la fórmula (II):



(II).

33. Un método para sintetizar un compuesto que comprende:

a) tratar un compuesto de la Fórmula (V):



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en donde

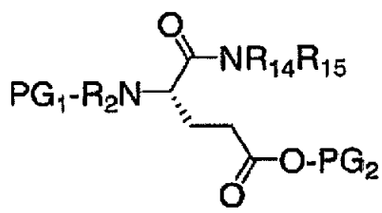
PG_1 es un grupo protector amina y PG_2 es un grupo protector de ácido carboxílico;

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), -$(CH_2)_nR_{11}$, -OH, o -O-alquilo (C_1-C_6);

R_{11} es arilo, heteroarilo, o cicloalquilo; y

n es 0-4;

con una amina, bajo condiciones efectivas para proporcionar un compuesto que tiene la fórmula (VI):



(VI)

en donde

R_{14} y R_{15} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, heterocicloalquil-$(CH_2)_n$-arilo, arilo bicíclico, arilo tricíclico, heteroarilo

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bicíclico, o heteroarilo tricíclico; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más R_{12}; o R_{14} y R_{15} juntos pueden formar un grupo cíclico de cinco- a siete-miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_{12} es hidrógeno, halógeno, -CN, $-OCF_3$, $-CF_3$, $-NO_2$, -OH, -SH, $-NR_7R_8$, $-CONR_7R_8$, $-NR_8COR_7$, $-NR_8CO_2R_7$, $-CO_2R_7$, $-COR_7$, $-SO_2$-alquilo (C_1-C_6), $-SO_2$-arilo, $-SO_2$-heteroarilo, $-SO_2R_7$, $-NR_7SO_2R_8$, $-SO_2NR_7R_8$; alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH- cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-(C_1- C_6) alquilo sustituido con arilo, arilo, heteroarilo, $-(CH_2)_n$-arilo, $-(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco-

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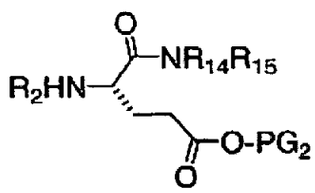
a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S; y

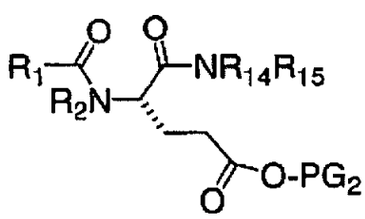
R_{13} es halógeno, -O-alquilo (C_1-C_6), $-CO_2H$, -OH, $-CF_3$, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con $-NH_2$, arilo sustituido con -O- alquilo (C_1-C_6), $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo;

b) hidrolizar el grupo protector amina de un compuesto de la Fórmula (VI), bajo condiciones efectivas para proporcionar un compuesto que tiene la fórmula (VII):



(VII);

c) tratar el compuesto de la Fórmula (VII) con un ácido carboxílico, bajo condiciones efectivas para proporcionar un compuesto que tiene la fórmula (VIII):



(VIII);

en donde

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R_1 es fenilo, heteroarilo, bifenilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada uno se sustituye opcionalmente con uno o más de R_5 o R_6, y cuando R_1 se sustituye con más de uno de R_5 o R_6, los sustituyentes pueden ser idénticos o diferentes;

R_5 es arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, -S-heteroarilo, -NH-arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO-arilo, -CO-heteroarilo, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2NH-arilo, -SO_2NH-heteroarilo, -$NHSO_2$-alquilo (C_1-C_6), -$NHSO_2$-arilo, -$NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R_5 se sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes; y

R_6 es hidrógeno, halógeno, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_7$, -CO_2R_7, -COR_7, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-

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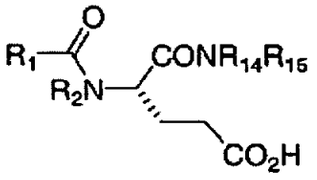
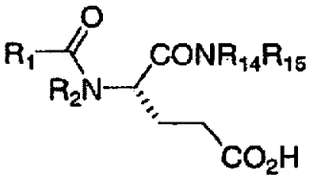
C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O- arilo, -O-heteroarilo, -S-arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13}; y

d) tratar el compuesto de la Fórmula (VIII) bajo condiciones efectivas para la hidrólisis del ácido carboxílico protegido, suministrando por lo tanto un compuesto que tiene la fórmula (II):



(II).

34. Un compuesto de la Fórmula (II):



(II).

se prepara por el método comprende:

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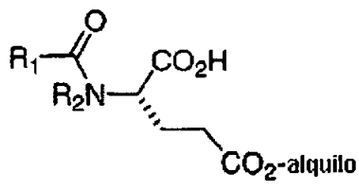
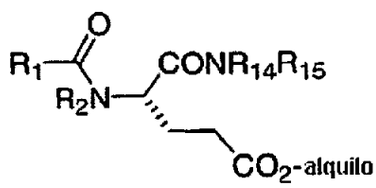
a) tratar un compuesto de la Fórmula (III):



(III)

con una amina, bajo condiciones efectivas para proporcionar un compuesto que tiene la fórmula (IV):



(IV);

b) tratar el compuesto de la Fórmula (IV) bajo condiciones efectivas para la hidrólisis del éster de alquilo, suministrando por lo tanto un compuesto que tiene la fórmula (II); en donde

R_1 es fenilo, heteroarilo, bifenilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada uno se sustituye opcionalmente con uno o más de R_5 o R_6, y cuando R_1 se sustituye con más de uno de R_5 o R_6, los sustituyentes pueden ser idénticos o diferentes;

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), $-(CH_2)_nR_{11}$, -OH, o -O-alquilo (C_1-C_6);

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R_5 es arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S- arilo, -S -heteroarilo, -NH-arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO-arilo, -CO-heteroarilo, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2NH-arilo, -SO_2NH-heteroarilo, -$NHSO_2$-alquilo (C_1-C_6), -$NHSO_2$-arilo, -$NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH- alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R_5 se sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes;

R_6 y R_{12} son cada uno independientemente hidrógeno, halógeno, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_{75}$ -CO_2R_7, -COR_7, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo,

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$-(CH_2)_n$-arilo, $-(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_{11} es arilo, heteroarilo, o cicloalquilo;

R_{13} es halógeno, -O-alquilo (C_1-C_6), $-CO_2H$, -OH, $-CF_3$, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con $-NH_2$, arilo sustituido con -O-alquilo (C_1-C_6), $-(CH_2)_n$-arilo, o $-(CH_2)_n$-heteroarilo;

R_{14} y R_{15} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, heterocicloalquil-$(CH_2)_n$-arilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, o heteroarilo

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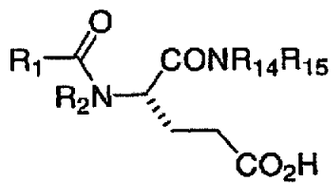
se sustituye opcionalmente con uno o más R_{12}; o R_{14} y R_{15} junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S; y

n es 0-4.

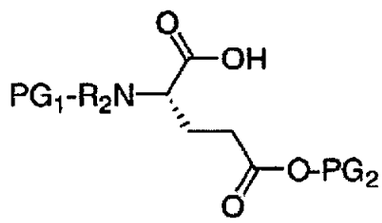
35. Un compuesto de la Fórmula (II):



(II).

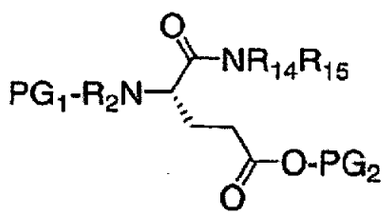
se prepara por el método comprende:

a) tratar un compuesto de la Fórmula (V):



(V)

con una amina, bajo condiciones efectivas para proporcionar un compuesto que tiene la fórmula (VI):



(VI);

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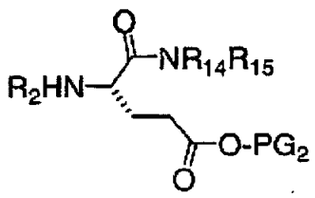
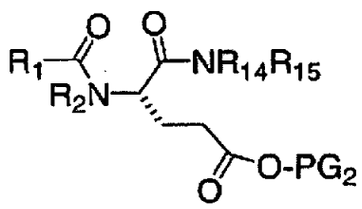
b) hidrolizar el grupo protector amina de un compuesto de la Fórmula (VI), bajo condiciones efectivas para proporcionar un compuesto que tiene la fórmula (VII):



(VII);

c) tratar el compuesto de la Fórmula (VII) con un ácido carboxílico, bajo condiciones efectivas para proporcionar un compuesto que tiene la fórmula (VIII):



(VIII);

d) tratar el compuesto de la Fórmula (VIII) bajo condiciones efectivas para la hidrólisis del ácido carboxílico protegido, suministrando por lo tanto un compuesto que tiene la fórmula (II); en donde

PG_1 es un grupo protector amina y PG_2 es un grupo protector de ácido carboxílico;

R_1 es fenilo, heteroarilo, bifenilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico, cada uno se sustituye opcionalmente con uno

o más de R_5 o R_6, y cuando R_1 se sustituye con más de uno de R_5 o R_6, los sustituyentes pueden ser idénticos o diferentes;

R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), -$(CH_2)_nR_{11}$, -OH, o -O-alquilo (C_1-C_6);

R_5 es arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S- arilo, -S -heteroarilo, -NH-arilo, -NH-heteroarilo, -CO-alquilo (C_1-C_6), -CO-arilo, -CO-heteroarilo, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2NH-arilo, -SO_2NH-heteroarilo, -$NHSO_2$-alquilo (C_1-C_6), -$NHSO_2$-arilo, -$NHSO_2$-heteroarilo, -NHCO-arilo, -NHCO-heteroarilo, -CONH-arilo, -CONH-heteroarilo, alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -NH- alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), o -CONH-cicloalquilo (C_3-C_6); cada alquilo, arilo, cicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más de R_6, y cuando R_5 se sustituye con más de uno de R_6, los sustituyentes pueden ser idénticos o diferentes;

R_6 y R_{12} son cada uno independientemente hidrógeno, halógeno, -CN, -OCF_3, -CF_3, -NO_2, -OH, -SH, -NR_7R_8, -$CONR_7R_8$, -NR_8COR_7, -$NR_8CO_2R_{75}$ -CO_2R_7, -COR_7, -SO_2-alquilo (C_1-C_6), -SO_2-arilo, -SO_2-heteroarilo, -SO_2R_7, -$NR_7SO_2R_8$, -$SO_2NR_7R_8$; alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -S-alquilo (C_1-C_6), -

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NH-alquilo (C_1-C_6), -NHCO-alquilo (C_1-C_6), -CONH-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -S-cicloalquilo (C_3-C_6), -NH-cicloalquilo (C_3-C_6), -NHCO-cicloalquilo (C_3-C_6), -CONH-cicloalquilo (C_3-C_6), heterocicloalquilo, -alquilo (C_1-C_6)-OR_7, alquinilo (C_2-C_6), alquenilo (C_2-C_6), -O-alquilo (C_1-C_6)-cicloalquilo (C_3-C_6), -O-alquenilo, -O-alquilo (C_1-C_6) sustituido con arilo, arilo, heteroarilo, -$(CH_2)_n$-arilo, -$(CH_2)_n$-heteroarilo, -O-arilo, -O-heteroarilo, -S-arilo, o -S-heteroarilo; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, alquenilo, o alquinilo se sustituye opcionalmente con uno o más de R_{13};

R_7 y R_8 son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, -$(CH_2)_n$-arilo, o -$(CH_2)_n$-heteroarilo; o R_7 y R_8 junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S;

R_{11} es arilo, heteroarilo, o cicloalquilo;

R_{13} es halógeno, -O-alquilo (C_1-C_6), -CO_2H, -OH, -CF_3, hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, cicloalquilo sustituido con -OH, arilo sustituido con -NH_2, arilo sustituido con -O-alquilo (C_1-C_6), -$(CH_2)_n$-arilo, o -$(CH_2)_n$-heteroarilo;

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R_{14} y R_{15} son cada uno independientemente hidrógeno, alquilo (C_1-C_6), arilo, heteroarilo, alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo, heterocicloalquil-$(CH_2)_n$- arilo, arilo bicíclico, arilo tricíclico, heteroarilo bicíclico, o heteroarilo tricíclico; cada alquilo, arilo, cicloalquilo, heterocicloalquilo, o heteroarilo se sustituye opcionalmente con uno o más R_{12}; o R_{14} y R_{15} junto con el átomo al cual ellos están adheridos pueden formar un grupo cíclico de cinco- a siete- miembros que contiene hasta 3 heteroátomos seleccionados de N, O, o S; y

n es 0-4.

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INHIBIDORES DE AGRECANASA GLUTAMATO

Resumen

La presente invención se relaciona con moduladores de la actividad metaloproteinasa.

Figura 1: Inhibición de degradación de agrecán mediante compuesto de ensayo 8OO

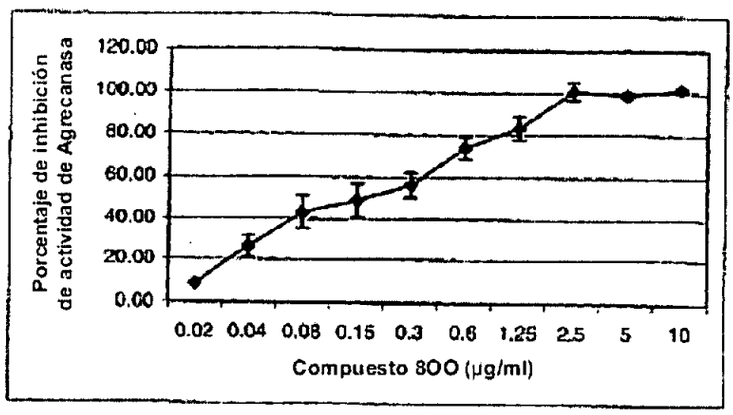
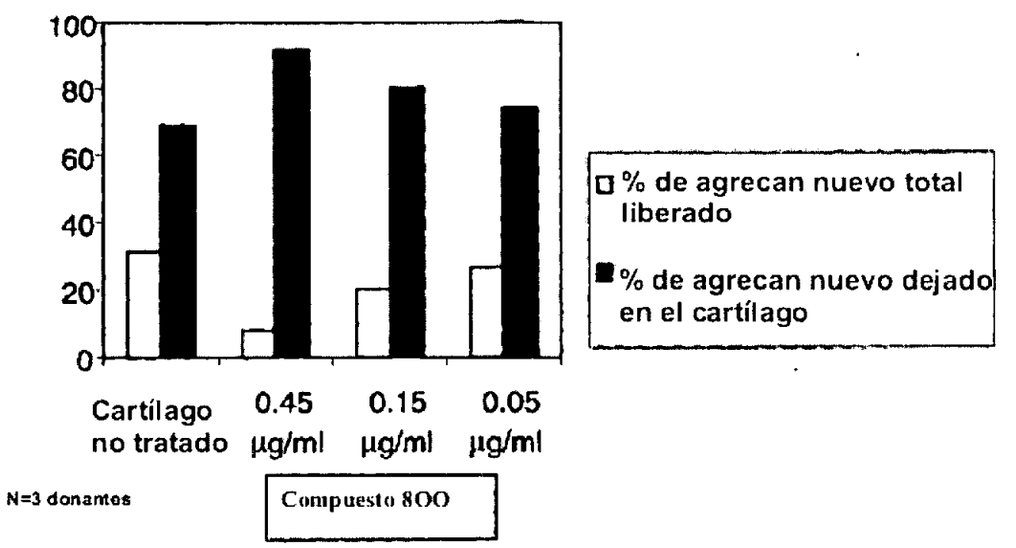


Figura 2: Compuesto de ensayo 8OO y metabolismo Agrecán



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.
0036119.00191WO1		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2006/027066	11/07/2006	11/07/2005
Applicant		
WYETH		

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 12 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. [ ] 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. [X] **Unity of invention is lacking** (see Box No III)

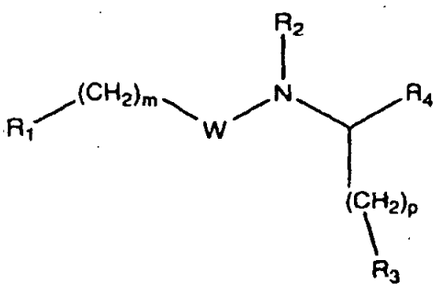
4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [ ] the text is approved as submitted by the applicant
   [X] 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. 1
      [X] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to compounds of the formula (I), which are modulators of metalloproteinase activity.



(I)

and pharmaceutically acceptable salts thereof,

wherein

W is –C(O)-, -OC(O)-, –NHC(O)-, -C(O)O-, or –C(O)NH-;

R_1 is phenyl, heteroaryl, biphenyl, bicyclic aryl, tricyclic aryl, bicyclic heteroaryl, or tricyclic heteroaryl, each optionally substituted with one or more of R_5 or R_6, and when R_1 is substituted with more than one of R_5 or R_6, the substituents can be identical or different;

R_2 is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -$(CH_2)_nR_{11}$, -OH, or -O-(C_1-C_6) alkyl;

R_3 is -CO_2H, -$CONH_2$, -CONHOH, -$CONHSO_2R_7$, tetrazole, -SO_2NHR_7, -SO_3H, -$PO(OH)NH_2$, -$PO(OH)OR_7$, -$CONHR_7$, -$COOR_7$, an acid mimetic group, or a 5 or 6-membered heterocycloalkyl or heteroaryl containing 1 to 4 heteroatoms selected from O, N, S;

R_4 is -CO_2H, -$CONH_2$, -$(CH_2)_nOR_7$, or -$CONR_9R_{10}$;

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C237/22 C07C235/84 C07D317/58 C07D333/24 C07D213/56
C07D277/30 C07C323/41 C07C259/06 C07C237/42 C07C231/16
A61K31/166 A61K31/36 A61K31/381 A61K31/4409 A61K31/426

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)

C07C C07D

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

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

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	TAKAHASHI K ET AL: "Novel matrix metalloproteinase inhibitors: Generation of lead compounds by the in silico fragment-based approach" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 13, no. 14, 15 July 2005 (2005-07-15), pages 4527-4543, XP004928368 ISSN: 0968-0896 page 4529, scheme 1 ----- -/--	1-3,7,8, 13,20, 22,23, 25-28, 30,31, 33-35

[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
18 April 2007	27/04/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seufert, Gudrun

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C237/22 C07C235/84 C07D317/58 C07D333/24 C07D213/56
C07D277/30 C07C323/41 C07C259/06 C07C237/42 C07C231/16
A61K31/166 A61K31/36 A61K31/381 A61K31/4409 A61K31/426

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)
C07C C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	TAKAHASHI K ET AL: "Novel matrix metalloproteinase inhibitors: Generation of lead compounds by the in silico fragment-based approach" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 13, no. 14, 15 July 2005 (2005-07-15), pages 4527-4543, XP004928368 ISSN: 0968-0896 page 4529, scheme 1 ----- -/--	1-3,7,8, 13,20, 22,23, 25-28, 30,31, 33-35

[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
18 April 2007	27/04/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seufert, Gudrun

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	F. MAKOVEC ET AL.: "Structure-Antigastrin Activity Relationships of New (R)-4-Benzamido-5-oxopentanoic Acid Derivatives" JOURNAL OF MEDICINAL CHEMISTRY, vol. 35, no. 1, 1992, pages 28-38, XP002413065 tables I,II	1-4,7,8, 13,14, 20,25, 26,34,35
X	J. R. PIPER, J. A. MONTGOMERY: "Syntheses of .alpha.- and .gamma.-substituted Amides, Peptides, and Esters of Methotrexate and Their Evaluation as Inhibitors of Folate Metabolism" JOURNAL OF MEDICINAL CHEMISTRY, vol 25, no. 2, 1982, pages 182-187, XP002413066 page 183, scheme I, compounds 4-6, 8, 10, 11, 15 table I, compounds MTX, 13a-13e; 14a-14d table II, compounds 7a-7c	1-3,7,8, 12,13, 20,25, 26,34,35
X	GB 1 108 819 A (ROTTA RES LAB S P A) 3 April 1968 (1968-04-03) claims; examples 1,3,5,8,9,11 table, compounds 236, 239, 249, 242, 246, 248, 251, 253, 279, 282, 283	1-3,7,8, 13,20, 25,26, 34,35
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002413080 Database accession no. BRN 3152508 abstract & GAUNT; WORMALL: BIOCHEM. J., 30, 1936, page 1915, 1922,	1,7,8,12
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& BUDEANU; DRUTA: AN. STIINT. UNIV.'AL. I. CUZA' IASI SECT. 1C, 10, 1964, pages 45, 46-51,	
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X	D. L. BOGER ET AL.: "Conformationally Restricted Analogues Designed for Selective Inhibition of GAR Tfase Versus Thymidylate Synthase or Dihydrofolate Reductase" BIOORG. MED. CHEM., vol. 8, no. 5, 2000, pages 1075-1086, XP002413067 page 1078, compounds 3a, 3b, 4a page 1079, compounds 4b, 4c, 3c tables 1,2	1-3,7,8, 12,13, 25,26
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-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	C. J. SPRINGER ET AL.: "Optimization of Alkylating Agent Prodrugs Derived from Phenol and Aniline Mustards: A New Clinical Candidate Prodrug (ZD2767) for Antibody-Directed Enzyme Prodrug Therapy (ADEPT)" JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 26, 1995, pages 5051-5065, XP002413068 table 1	1,3,7,8, 12
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X	D. J. AUGERI ET AL.: "Potent and Selective Non-Cysteine-Containing Inhibitors of Protein Farnesyltransferase" JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 22, 1998, pages 4288-4300, XP002413070 page 4298, right-hand column, last paragraph - page 4299, left-hand column, line 4; table 4	1,2,6-8, 12
X	WO 01/90077 A (GUILFORD PHARMACEUTICALS) 29 November 2001 (2001-11-29) page 19, compound 25, table III	1-3,5,7, 8,12,13, 15,20

-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SAKYO, KATSUFUMI ET AL: "Inhibitory effect of methotrexate on matrix metalloproteinase-1 (collagenase) production by synovial fibroblasts" XP002413088 retrieved from STN Database accession no. 1997:137341 abstract & OYO YAKURI, vol. 52, no. 6, 1996, pages 451-457,	1-3,7,8, 12,13, 22,23, 25-28, 30,31
A	WO 2005/060456 A2 (WYETH CORP [US]; MORRIS ELISABETH A [US]; GLASSON SONYA S [US]; XIANG) 7 July 2005 (2005-07-07) claims; examples	
A	WO 2005/058808 A (JAPAN TOBACCO INC [JP]; FRYER ANDREW M [US]; SHIOZAKI MAKOTO [JP]; LIT) 30 June 2005 (2005-06-30) claims; examples	
A	WO 00/27808 A (AVENTIS PHARMA GMBH [DE]) 18 May 2000 (2000-05-18) claims; examples	
A	WO 01/83445 A (SAMSUNG ELECTRONICS CO LTD [KR]; PARK YOUNG JUN [KR]; RYU CHOON HO [KR]) 8 November 2001 (2001-11-08) claims; examples	
X	U. KUEFNER ET AL.: "Carboxypeptidase-Mediated Release of Methotrexate from Methotrexate .alpha.-Peptides" BIOCHEMISTRY, vol. 28, no. 5, 1989, pages 2288-2297, XP002429817 page 2290, left-hand column, line 6 - right-hand column, line 21	32
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-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. F. KERWIN, JR. ET AL: "Hybrid Cholecystokinin (CCK) Antagonist: New Implications in the Design and Modification of CCK Antagonists" J. MED. CHEM., vol. 32, no. 4, 1989, pages 739-742, XP002429816 page 740, left-hand column, line 3 - line 15 page 740, right-hand column, line 12 - line 15 page 740, right-hand column, line 37 - line 39	33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/027066

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

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

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 22-24 and 27-31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-31, 34, 35

Compounds of formula (I) and (II), methods for their use and compositions comprising them

---

2. claim: 32

Process for the preparation of compounds of formula II starting from compounds of formula (III) via compounds of formula (IV)

---

3. claim: 33

Process for the preparation of compounds of formula (II) starting from a compound of formula (V) via compounds (VI), (VII) and (VIII)

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 0183445 A		EP 1189882 A1	27-03-2002
		JP 2003531894 T	28-10-2003

736

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/US2006/027066	11.07.2006	11.07.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07C237/22 C07C235/84 C07D317/58 C07D333/24 C07D213/56 C07D277/30 C07C323/41 C07C259/06 C07C237/42 C07C231/16 A61K31/166 A61K31/36 A61K31/381 A61K31/4409 A61K31/426 A61P19/00

Applicant
WYETH

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 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

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 D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Seufert, Gudrun Telephone No. +49 89 2399-8330

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/027066

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. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto 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.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-10(part), 12-31(part), 34(part), 35(part)

because:

☒ the said international application, or the said claims Nos. 22-24(part), 27-31(part) relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-10(part), 12-31(part), 34(part), 35(part)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/027066

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☒ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

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	9-11, 17-19, 21, 24, 29
	No:	Claims	1-8, 12-16, 20, 22-23, 25-28, 30-35
Inventive step (IS)	Yes:	Claims	11
	No:	Claims	1-10, 12-35
Industrial applicability (IA)	Yes:	Claims	1-21, 25, 26, 32-35
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2006/027066

Reference is made to the following documents:

D1: BIOORGANIC & MEDICINAL CHEMISTRY, vol. 13, no. 14, 15 July 2005, pages 4527-4543
D2: JOURNAL OF MEDICINAL CHEMISTRY, vol. 35, no. 1, 1992, pages 28-38
D3: JOURNAL OF MEDICINAL CHEMISTRY, vol. 25, no. 2, 1982, pages 182-187
D4: GB-A-1 108 819
D5: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 3152508
D6: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 3149561
D7: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 2790059
D8: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 9663820
D9: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 3210937
D10: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 2600925
D11: BIOORG. MED. CHEM., vol. 8, no. 5, 2000, pages 1075-1086
D12: US-A-2 440 649
D13: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 55943
D14: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 2894932
D15: JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 26, 1995, pages 5051-5065
D16: JOURNAL OF MEDICINAL CHEMISTRY, vol. 22, no. 7, 1979, pages 869-874
D17: JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 22, 1998, pages 4288-4300
D18: WO 01/90077 A
D19: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 1997:137341
D20: WO 2005/060456 A2
D21: WO 2005/058808 A
D22: WO 00/27808 A
D23: WO 01/83445 A
D24: BIOCHEMISTRY, vol. 28, no. 5, 1989, pages 2288-2297
D25: EUR. J. MED. CHEM. - CHIM. THER., vol. 21, no. 1, 1986, pages 9-22

D26: J. AM. CHEM. SOC., vol.. 32, no. 4, 1989, pages 739-742

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 The initial phase of the search of the first invention revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of claims.

The search was restricted to compounds of claim 11, and to compounds of claim 19 as far as they refer to glutamine, glutamic acid und glutaminamide derivatives of formula (I) or (II) whereby R_4 is CO_2H, $CONH_2$ or $CONR_9R_{10}$; R^3 is CO_2H, $CONH_2$, CONHOH, $CONSO_2R_7$, $CONHR_7$ or $COOR_7$; p is 2, W is CO and R_1 is as defined in claims 14-16.

Compounds which are mentioned in the search report and which fall outside the restricted scope of the search are merely an arbitrary selection from the very large amount of documents relevant to the issue of novelty.

III.2 Claims 22-24 and 27-31 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

IV. Lack of unity of invention

This Authority considers that there are 3 inventions covered by the claims indicated as follows:

A: Claim 1-31, 34 and 35 directed to compounds of formula (I) and (II), methods for their use and compositions comprising them.

B: Claim 32 directed to a process for the preparation of compounds of formula II starting from compounds of formula (III) via compounds of formula (IV).

C: Claim 33 directed to a process for the preparation of compounds of formula II starting from a compound of formula (V) via compounds (VI), (VII) and (VIII).

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The problem to be solved by the present application was the provision of further compounds, which are useful as metalloproteinase modulators. The problem was allegedly solved by compounds of formula (I) and (II), whereby the compounds of formula (II) are almost entirely encompassed by formula (I), and the provision of two different methods for the preparation of compounds of formula (II). However, compounds of formula (II) are not at all new, see documents D1-D4, D7-D9, D16 and D18 (Attention is drawn to the fact that the documents D1-D4, D7-D9, D16 and D18 merely an arbitrary selection of the large number of documents relevant to the issue of novelty of formula (II)). There is thus no common novel feature linking the two processes and the compounds. Furthermore, with the compounds of formula (II) being known in the prior art, there is no common novel feature between the two different processes. The special technical feature in the first process is the reaction sequence of amidation and hydrolysis starting with a compound of formula (III). The special technical feature in the second process is the reaction sequence of amidation, deprotection, acylation and hydrolysis starting with a compound of formula (V). The reaction sequences and the starting material are different. Thus, the special technical features of the two different processes are neither the same nor corresponding.

The present application in actual fact solves three different problems. One is the provision of further compounds and their use as metalloproteinase modulators, the second is the provision of a further process for the known compounds of formula (II), and the third problem is the provision of an even further process for the preparation of compounds of formula (II). The solutions to these problems do not share a

common novel technical feature, and the special technical features are neither the same nor corresponding as set out above. Additionally, these problems can be solved independently of each other.

In conclusion, the groups of claims are not linked by common or corresponding special technical features and define 3 different inventions not linked by a single general inventive concept. The application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

V. Reasoned statement with regard to novelty, inventive step or industrial applicability

V.1 First invention

Novelty

Claim 1 of the present application refers to compounds of the general formula (I). Compounds which fall within the scope of this formula are known in the art, see the documents D1-D19 and the cited passages in the International search report. Claim 1 as well as the dependent claims 2-8 and 12-16 are therefore not considered to meet the requirement of Art. 33(2) PCT. Attention is drawn to the fact that D1 was available online the 23.05.2005, see D1, statement below the names of the authors, which is well before the priority date of the present application. This document is therefore considered to be prior art in the sense of Rule 64.1 for the purpose of Art. 33(2) and (3) PCT.

Claim 20 of the present application refers to compounds of the general formula (II). Compounds falling within the scope of formula (II) are known in the art, see the documents D1-D4, D7-D9, D16 and D18 and the cited passages in the International search report. Claim 20, therefore, does not comply with the requirement of Art. 33(2) PCT. Claims 34 and 35 refer to compounds of formula (II) prepared according to the methods of claim 32 or 33. Such a claim refers to the compounds per se. The preparation methods are not considered to be limiting. Thus, the subject-matter of

claims 34 and 35 is also anticipated by the documents D1-D4, D7-D9, D16 and D18 (Art. 33(2) PCT).

The presently claimed compounds of formula (I) and (II) are useful for modulating the activity of a metalloproteinase or an aggrecanase. Documents D1 and D19 disclose compounds falling within the scope of formula (I) and/or (II) and their metalloproteinasemodulating activity. The subject-matter of claims 22, 23, 25-28, 30 and 31 is therefore not novel in view of D1 and D19 contrary to the requirement of Art. 33(2) PCT.

Claim 25 refers to a pharmaceutical composition comprising a compound of formula (I) or (II). Such a claim may be considered as novel if no pharmaceutical activity has been disclosed for the compounds. However, documents D1-D4, D11, D12, D16 and D19 describe compounds falling within the scope of formula (I) and/or (II) and their pharmaceutical activity. In addition the documents D4 and D12 refer directly to pharmaceutical compositions, see D4, claim 13 and D12, column, 2, lines 21-28. Therefore, the subject-matter of claim 25 and dependent claim 26 does not meet the requirement of Art. 33(2) PCT.

Claims 9-11, 17-19, 21, 24 and 29 appear to meet the requirement of Art. 33(2) PCT in view of the available prior documents D1-D23. It should however be noted that the search has been limited for the reasons set out above.

Inventive step

The presently claimed subject-matter as far as it is novel is not considered to be inventive in view of the novelty destroying documents D1-D19, especially in view of the documents D1 and D19, which refer to compounds of the present invention for the same use, i.e. metalloproteinase modulators.

Furthermore, all of the presently prepared and tested examples belong to the group of glutamine, glutamic acid or glutaminamide compounds. Apparently, the glutamine, glutamic acid or glutaminamide structures are an essential feature for the desired

activity. Claim 1, however, is not limited to this type of structures, for example when R_3 = tetrazol, SO_2NHR^7, SO_3H, $PO(OH)NH_2$, $PO(OH)OR_7$, acid mimetic group, heterocycloalkyl or heteroaryl; or $R_4 = (CH_2)_nOR_7$. Furthermore, in all of the prepared and tested compounds is the variable W a C(O) group.
It is common general knowledge that even small structural modifications may change the biological activity significantly. It is therefore not credible that basically all compounds of the present invention, especially those which differ in their structure from the tested compounds, will exhibit the desired activity and thus solve the underlying technical problem of providing further metalloproteinase modulating compounds.

The subject-matter of the claims 1-10, 12-31, 34 and 35 is therefore not considered as involving an inventive step contrary to the requirement of Art. 33(3) PCT.

The subject-matter of claim 11 appears to meet the requirement of Art. 33(3) PCT.

Additionally, attention is drawn to the fact that in order for a claim to compounds using a Markush formula to be regarded as uniform, the claimed compounds should have in common a structural moiety which is distinctive in view of the prior art. The structural moiety common to all the present compounds is the N-CH-$(CH_2)_p$- unit, whereby the CH group is attached to a further substituent. However, such a moiety is to be found in the compounds according to D1. D1 even discloses compounds with the glutamine unit. The compounds of claim 1, therefore, lack unity of invention. The same applies for the compounds of claim 20.

Industrial applicability

For the assessment of the present claims 22-24 and 27-31 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however,

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2006/027066

Reference is made to the following documents:

D1: BIOORGANIC & MEDICINAL CHEMISTRY, vol. 13, no. 14, 15 July 2005, pages 4527-4543
D2: JOURNAL OF MEDICINAL CHEMISTRY, vol. 35, no. 1, 1992, pages 28-38
D3: JOURNAL OF MEDICINAL CHEMISTRY, vol. 25, no. 2, 1982, pages 182-187
D4: GB-A-1 108 819
D5: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 3152508
D6: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 3149561
D7: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 2790059
D8: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 9663820
D9: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 3210937
D10: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 2600925
D11: BIOORG. MED. CHEM., vol. 8, no. 5, 2000, pages 1075-1086
D12: US-A-2 440 649
D13: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 55943
D14: DATABASE BEILSTEIN, BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Database accession no. BRN 2894932
D15: JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 26, 1995, pages 5051-5065
D16: JOURNAL OF MEDICINAL CHEMISTRY, vol. 22, no. 7, 1979, pages 869-874
D17: JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 22, 1998, pages 4288-4300
D18: WO 01/90077 A
D19: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 1997:137341
D20: WO 2005/060456 A2
D21: WO 2005/058808 A
D22: WO 00/27808 A
D23: WO 01/83445 A
D24: BIOCHEMISTRY, vol. 28, no. 5, 1989, pages 2288-2297
D25: EUR. J. MED. CHEM. - CHIM. THER., vol. 21, no. 1, 1986, pages 9-22

D26: J. AM. CHEM. SOC., vol.. 32, no. 4, 1989, pages 739-742

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 The initial phase of the search of the first invention revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of claims.

The search was restricted to compounds of claim 11, and to compounds of claim 19 as far as they refer to glutamine, glutamic acid und glutaminamide derivatives of formula (I) or (II) whereby R_4 is CO_2H, $CONH_2$ or $CONR_9R_{10}$; R^3 is CO_2H, $CONH_2$, CONHOH, $CONSO_2R_7$, $CONHR_7$ or $COOR_7$; p is 2, W is CO and R_1 is as defined in claims 14-16.

Compounds which are mentioned in the search report and which fall outside the restricted scope of the search are merely an arbitrary selection from the very large amount of documents relevant to the issue of novelty.

III.2 Claims 22-24 and 27-31 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

IV. Lack of unity of invention

This Authority considers that there are 3 inventions covered by the claims indicated as follows:

A: Claim 1-31, 34 and 35 directed to compounds of formula (I) and (II), methods for their use and compositions comprising them.

B: Claim 32 directed to a process for the preparation of compounds of formula II starting from compounds of formula (III) via compounds of formula (IV).

C: Claim 33 directed to a process for the preparation of compounds of formula II starting from a compound of formula (V) via compounds (VI), (VII) and (VIII).

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The problem to be solved by the present application was the provision of further compounds, which are useful as metalloproteinase modulators. The problem was allegedly solved by compounds of formula (I) and (II), whereby the compounds of formula (II) are almost entirely encompassed by formula (I), and the provision of two different methods for the preparation of compounds of formula (II). However, compounds of formula (II) are not at all new, see documents D1-D4, D7-D9, D16 and D18 (Attention is drawn to the fact that the documents D1-D4, D7-D9, D16 and D18 merely an arbitrary selection of the large number of documents relevant to the issue of novelty of formula (II)). There is thus no common novel feature linking the two processes and the compounds. Furthermore, with the compounds of formula (II) being known in the prior art, there is no common novel feature between the two different processes. The special technical feature in the first process is the reaction sequence of amidation and hydrolysis starting with a compound of formula (III). The special technical feature in the second process is the reaction sequence of amidation, deprotection, acylation and hydrolysis starting with a compound of formula (V). The reaction sequences and the starting material are different. Thus, the special technical features of the two different processes are neither the same nor corresponding.

The present application in actual fact solves three different problems. One is the provision of further compounds and their use as metalloproteinase modulators, the second is the provision of a further process for the known compounds of formula (II), and the third problem is the provision of an even further process for the preparation of compounds of formula (II). The solutions to these problems do not share a

common novel technical feature, and the special technical features are neither the same nor corresponding as set out above. Additionally, these problems can be solved independently of each other.

In conclusion, the groups of claims are not linked by common or corresponding special technical features and define 3 different inventions not linked by a single general inventive concept. The application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

V. Reasoned statement with regard to novelty, inventive step or industrial applicability

V.1 First invention

Novelty

Claim 1 of the present application refers to compounds of the general formula (I). Compounds which fall within the scope of this formula are known in the art, see the documents D1-D19 and the cited passages in the International search report. Claim 1 as well as the dependent claims 2-8 and 12-16 are therefore not considered to meet the requirement of Art. 33(2) PCT. Attention is drawn to the fact that D1 was available online the 23.05.2005, see D1, statement below the names of the authors, which is well before the priority date of the present application. This document is therefore considered to be prior art in the sense of Rule 64.1 for the purpose of Art. 33(2) and (3) PCT.

Claim 20 of the present application refers to compounds of the general formula (II). Compounds falling within the scope of formula (II) are known in the art, see the documents D1-D4, D7-D9, D16 and D18 and the cited passages in the International search report. Claim 20, therefore, does not comply with the requirement of Art. 33(2) PCT. Claims 34 and 35 refer to compounds of formula (II) prepared according to the methods of claim 32 or 33. Such a claim refers to the compounds per se. The preparation methods are not considered to be limiting. Thus, the subject-matter of

claims 34 and 35 is also anticipated by the documents D1-D4, D7-D9, D16 and D18 (Art. 33(2) PCT).

The presently claimed compounds of formula (I) and (II) are useful for modulating the activity of a metalloproteinase or an aggrecanase. Documents D1 and D19 disclose compounds falling within the scope of formula (I) and/or (II) and their metalloproteinasemodulating activity. The subject-matter of claims 22, 23, 25-28, 30 and 31 is therefore not novel in view of D1 and D19 contrary to the requirement of Art. 33(2) PCT.

Claim 25 refers to a pharmaceutical composition comprising a compound of formula (I) or (II). Such a claim may be considered as novel if no pharmaceutical activity has been disclosed for the compounds. However, documents D1-D4, D11, D12, D16 and D19 describe compounds falling within the scope of formula (I) and/or (II) and their pharmaceutical activity. In addition the documents D4 and D12 refer directly to pharmaceutical compositions, see D4, claim 13 and D12, column, 2, lines 21-28. Therefore, the subject-matter of claim 25 and dependent claim 26 does not meet the requirement of Art. 33(2) PCT.

Claims 9-11, 17-19, 21, 24 and 29 appear to meet the requirement of Art. 33(2) PCT in view of the available prior documents D1-D23. It should however be noted that the search has been limited for the reasons set out above.

Inventive step

The presently claimed subject-matter as far as it is novel is not considered to be inventive in view of the novelty destroying documents D1-D19, especially in view of the documents D1 and D19, which refer to compounds of the present invention for the same use, i.e. metalloproteinase modulators.

Furthermore, all of the presently prepared and tested examples belong to the group of glutamine, glutamic acid or glutaminamide compounds. Apparently, the glutamine, glutamic acid or glutaminamide structures are an essential feature for the desired

activity. Claim 1, however, is not limited to this type of structures, for example when R_3 = tetrazol, SO_2NHR^7, SO_3H, $PO(OH)NH_2$, $PO(OH)OR_7$, acid mimetic group, heterocycloalkyl or heteroaryl; or $R_4 = (CH_2)_nOR_7$. Furthermore, in all of the prepared and tested compounds is the variable W a C(O) group.
It is common general knowledge that even small structural modifications may change the biological activity significantly. It is therefore not credible that basically all compounds of the present invention, especially those which differ in their structure from the tested compounds, will exhibit the desired activity and thus solve the underlying technical problem of providing further metalloproteinase modulating compounds.

The subject-matter of the claims 1-10, 12-31, 34 and 35 is therefore not considered as involving an inventive step contrary to the requirement of Art. 33(3) PCT.

The subject-matter of claim 11 appears to meet the requirement of Art. 33(3) PCT.

Additionally, attention is drawn to the fact that in order for a claim to compounds using a Markush formula to be regarded as uniform, the claimed compounds should have in common a structural moiety which is distinctive in view of the prior art. The structural moiety common to all the present compounds is the N-CH-$(CH_2)_p$- unit, whereby the CH group is attached to a further substituent. However, such a moiety is to be found in the compounds according to D1. D1 even discloses compounds with the glutamine unit. The compounds of claim 1, therefore, lack unity of invention. The same applies for the compounds of claim 20.

Industrial applicability

For the assessment of the present claims 22-24 and 27-31 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however,

claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

There are no objections with regard to the industrial applicability of the subject-matter of claims 1-21, 25, 26, 34 and 35.

V.II Second invention

Novelty

Claim 32 refers to a method for the preparation of compounds of the formula (II) starting from compounds of formula (III) via compounds of formula (IV). Documents D24 and D25 disclose such a reaction sequence for the type of compounds of formula (II), see D24, page 2290, left-hand column, line 6 - right-hand column, line 21 and D25, page 19, scheme 2 and left-hand column, last paragraph - right-hand column, line 32. A novel teaching is thus not apparent (Art. 33(2) PCT).

Inventive step

Even if novelty would have to be acknowledged for purly formal reasons, the subject-matter of claim 32 is not considered to meet the requirement of Art. 33(3) PCT. D24 and D25 clearly teach the same reaction sequence for the type of compounds of formula (II). The process of claim 32 is therefore merely an analogy process, which would only comply with the requirement of novelty and inventive step in combination with novel and inventive compounds (Art. 33(3) PCT).

Industrial applicability

There are no objections against the industrial applicablity.

V.III Third invention

Novelty

Claim 33 refers to a process for the preparation of compounds of formula II starting from a compound of formula (V) via compounds (VI), (VII) and (VIII). Such a reaction sequence for compounds of formula (II) is known in the art, see document D1, page 4529, scheme 1, and document D26, page 740, left-hand column, lines 3-15, right hand column, lines 12-15 and 37-39. The subject-matter of claim 33 is therefore not considered to meet the requirement of Art. 33(2) PCT.

Inventive step

The subject-matter of claim 33, as far as it is novel, is not considered as involving an inventive step. For this subject-matter claim 33 merely represents an analogy process, which does not require inventive skills and is only considered to meet the requirement Art. 33(3) in combination with new and inventive compounds.

Industrial applicability

There are no objections against the industrial applicablity.

Further objections:

1. The claims are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefor are the following: Claim 1 as well as claim 20 encompass a large amount of compounds, while only a small part is supported by the description. Especially biological data showing that the technical problem is solved over basically the whole scope of the claim are available for only a small part of the compounds.

2. The definitions of the variables are inconsistent within the claims and inconsistent with the definitions of these variables in the description, see pages 6-11. For example:

- All groups, such as alkyl, alkenyl, aryl, heteroaryl, etc., may be substituted, see page 6, paragraph 16, which means substituted by any substituent. In the claims these groups are sometimes unsubstituted (see R_2 in formula (I)) or substituted by certain substituents.
- The terms "aryl" or "heteroaryl" commonly refers to aromatic cyclic or heterocyclic ring systems. They do not include compounds with an aromatic cyclic or heterocyclic ring, whereby these rings are fused with non aromatic carbocyclic or heterocyclic rings. The same applies for the terms "bicyclic and tricyclic aryl or heteroaryl", see page 10, paragraph 27 - page 11, paragraph 30.
- Commonly the terms "aryl" and "heteroaryl" include mono and polycyclic structures (see also description page 9, paragraph 24 and page 8, paragraph 22). However, the use of the terms "bicyclic or tricyclic aryl or heteroaryl" leads to the impression that other polycyclic groups were not meant to be included.
- The term "heterocycloalkyl" does not include unsaturated rings as mentioned on page 8, paragraph 23.

These inconsistencies lead to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

3. The term "acid mimetic group" has no well-recognised meaning and leaves the reader in doubt as to the exact scope of the claim 1, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.

4. The residues mentioned in the dependent claim 10 for the variable R_5 are not included in claim 1. Aryl and heteroaryl or bicyclic and tricyclic aryl or heteroaryl (see claim 1) commonly refer to aromatic cyclic or heterocyclic ring systems. They do not include compounds with an aromatic cyclic or heterocyclic ring, whereby these rings are fused with non aromatic carbocyclic or heterocyclic rings.
The same objection is raised for the dependent claims 14, 15 and 21.

5. The following compound "3-[(biphenyl-4-methyl)amino]-3-oxopropanoic acid" (see claim 21, page 247, fourth compound from the bottom of the page) does not fall within the scope of formula (I).

6. Claims 34 and 35 are identical to claim 20. They are thus superfluous (Art. 6 PCT, conciseness)

7. The vague and imprecise statement in the description on page 234, paragraph 1000 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.

8. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D19 and D20-D26 is not mentioned in the description, nor are these documents identified therein.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

SUPERKO, Colleen
WILMER CUTLER PICKERING HALE AND DORR LLP
60 State Street
Boston, MA 02109
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 06 October 2006 (06.10.2006)	
Applicant's or agent's file reference 0036119.00191WO1	**IMPORTANT NOTIFICATION**
International application No. PCT/US2006/027066	International filing date *(day/month/year)* 11 July 2006 (11.07.2006)
International publication date *(day/month/year)* **Not yet published**	Priority date *(day/month/year)* 11 July 2005 (11.07.2005)
Applicant WYETH et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)***An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
11 July 2005 (11.07.2005)	60/697,590	US	14 September 2006 (14.09.2006)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Dorothée Mülhausen
Facsimile No. +41 22 338 87 40
Telephone No. +41 22 338 96 72

751

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

SUPERKO, Colleen
Wilmer Cutler Pickering Hale and Dorr LLP
1875 Pennsylvania Avenue, NW
Washington, DC 20006
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
11 September 2007 (11.09.2007)

Applicant's or agent's file reference
0036119.00191WO1

IMPORTANT NOTIFICATION

International application No.
PCT/US2006/027066

International filing date *(day/month/year)*
11 July 2006 (11.07.2006)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
SABATINI, Joshua, James
12 Old Mamaroneck Road, Apt. #5e
White Plains, NY 106065
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

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
SABATINI, Joshua, James
12 Old Mamaroneck Road, Apt. 7G
White Plains, NY 10605
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:
The indication of a new address of the applicant SABATINI, Joshua, James on the demand has been considered as a request for recording a change under Rule 92bis. In case of disagreement, the International Bureau should be notified immediately

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ 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

Facsimile No. +41 22 338 87 40

Authorized officer
Mena Ana
e-mail pt01.pct@wipo.int
Telephone No. +41 22 338 74 01

WILMER CUTLER PICKERING HALE AND DORR LLP
752
SEP 4 2007
DOCKET DEPT.
INTELLECTUAL PROPERTY DEPARTMENT

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

JACOB STEVEN OYLOE
WILMER CUTLER PICKERING HALE AND DORR LLP
1875 PENNSYLVANIA AVENUE, NW
WASHINGTON, DISTRICT OF COLUMBIA 20006

PCT

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)*	10 Aug 2007
Applicant's or agent's file reference: 0036119.00191W01	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2006/027066	11 Jul 2006	11 Jul 2005

Applicant: WYETH

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

   26 Jul 2007

2. That date of receipt is:

   ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).

   ☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(c)).

   ☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **after** the expiration of 19 months from the priority date. Consequently, in respect of some Offices, the demand does not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)) and the acts for entry into the national phase must therefore be performed within 20 months from the priority date (or later in some Offices). **However**, in respect of some other Offices, the time limit of 30 months (or later) may nevertheless apply. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

   ☐ *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

RECEIVED
OCT 03 2007
SHEILA McBRIDE

Name and mailing address of the IPEA/	Authorized officer
Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450	Misty Walker WILMER CUTLER PICKERING HALE AND DORR LLP DOCKETING
Facsimile No. 571-273-3201	Telephone No. 703-308-9290 EXT 122

Form PCT/IPEA/402 (April 2002; reprint January 2004)

RE: 3649.191W01
Action Date:
Action to be Taken:
Docketed By: 9/7/07

Industria y Comercio
SUPERINTENDENCIA

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

(21) N° de solicitud:	(51) Int Cl: **C07C 237/22, C07C 237/42, C07C 235/84, C07C 231/16, C07D 317/58, A61K 31/166, C07D 333/24, A61K 31/36, C07D 213/56, A61K 31/381, C07D 277/30, A61K31/4409, C07C 323/41, A61K 31/426, C07C 259/06**
22) Fecha de solicitud:	(71)Solicitante(s) **WYETH**
(30) Prioridad (31) ***No.*** **60/697,590** 32) ***Fecha*** **11/07/05** (33) ***País*** **US**	(72) Inventor(es) **SUM, Phaik-Eng** **HOW, David, Brian** **y otros**
	(74) Apoderado: **ALVARO CORREA ORDOÑEZ**
(85) Fecha límite inicio fase nacional: ***11/02/08*** (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: **11/07/06** No. de solicitud **PCT/US2006/027066**	(87) Publicación internacional Fecha: **18/01/07** N° publicación: **WO/2007/008994**

(54) Título: **INHIBIDORES DE AGRECANASA GLUTAMATO**

Reivindicación(es):

1. La presente invención se relaciona con los compuestos de fórmula (I), los cuales son moduladores de la actividad de la metaloproteinasa y las sales farmacéuticamente aceptables de estos, en donde W es -C(O)-, -OC(O)-, -NHC(O)-, -C(O)O-, o -C(O)NH-; R_1 es fenilo, heteroarilo, bifenilo, arilo biciclico, arilo triciclico, heteroarilo biciclico, o heteroarilo triciclico, cada uno se sustituye opcionalmente con uno o más de R_5 o R_6, y cuando R_1 se sustituye con más de uno de R_5 o R_6, los sustituyentes pueden ser idénticos o diferentes; R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), -$(CH_2)nR_{11}$, -OH, o -O-alquilo (C_1-C_6); R_3 es -CO_2H, -$CONH_2$, -CONHOH, -$CONHSO_2R_7$, tetrazol, -SO_2NHR_7, -SO_3H, -$PO(OH)NH_2$, -$PO(OH)OR_7$, -$CONHR_7$, -$COOR_7$, un grupo de ácido mimético, o un heterocicloalquilo de 5 o 6 miembros o heteroarilo que contiene 1 a 4 heteroátomos seleccionados de O, N, S; R_4 es -CO_2H, -$CONH_2$, -(CH2)nOR7, o -$CONR_9R_{10}$

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Industria y Comercio
SUPERINTENDENCIA

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

PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

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

(51) Clasificación Internacional C07C 237/22, C07C 237/42, C07C 235/84, C07C 231/16, C07D 317/58, A61K 31/166, C07D 333/24, A61K 31/36, C07D 213/56, A61K 31/381, C07D 277/30, A61K31/4409, C07C 323/41, A61K 31/426, C07C 259/06

(71)Solicitante(s) **WYETH**

(72) Inventor(es) SUM, Phaik-Eng; HOW, David, Brian; SABATINI, Joshua, James; XIANG, Jason, Shaoyun; IPEK, Manus y FEYFANT, Eric

(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

(30) Prioridad	(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
	60/697,590	**11/07/05**	**US**

(85) Fecha inicio fase nacional: **11/02/08**

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: **11/07/06**
No. de solicitud **PCT/US2006/027066**

(87) Publicación internacional
Fecha: ***18/01/07***
N° publicación: **WO 2007/008994**

(54) Titulo: **INHIBIDORES DE AGRECANASA GLUTAMATO**

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Industria y Comercio

SUPERINTENDENCIA

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

SUPERINTENDENCIA PATENTE DE INVENCION ____ PCT X MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

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

(51) Clasificación Internacional : C07C 237/22, C07C 237/42, C07C 235/84, C07C 231/16, C07D 317/58, A61K 31/166, C07D 333/24, A61K 31/36, C07D 213/56, A61K 31/381, C07D 277/30, A61K31/4409, C07C 323/41, A61K 31/426, C07C 259/06

(71)Solicitante(s) **WYETH**

(72) Inventor(es) SUM, Phaik-Eng; HOW, David, Brian; SABATINI, Joshua, James; XIANG, Jason, Shaoyun; IPEK, Manus y FEYFANT, Eric

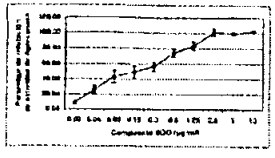
(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
	60/697,590	**11/07/05**	**US**

(85) Fecha límite inicio fase nacional: **11/02/08**

(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: **11/07/06**
No. de solicitud **PCT/US2006/027066**

(87) Publicación internacional:
Fecha: ***18/01/07***
No. Publicación : **WO 2007/008994**



(54) Título: **INHIBIDORES DE AGRECANASA GLUTAMATO**

(57) Resumen: La presente invención se relaciona con los compuestos de fórmula (I), los cuales son moduladores de la actividad de la metaloproteinasa y las sales farmacéuticamente aceptables de estos, en donde W es -C(O)-, -OC(O)-, -NHC(O)-, -C(O)O-, o -C(O)NH-; R_1 es fenilo, heteroarilo, bifenilo, arilo biciclico, arilo triciclico, heteroarilo biciclico, o heteroarilo triciclico, cada uno se sustituye opcionalmente con uno o más de R_5 o R_6, y cuando R_1 se sustituye con más de uno de R_5 o R_6, los sustituyentes pueden ser idénticos o diferentes; R_2 es hidrógeno, alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), -$(CH_2)nR_{11}$, -OH, o -O-alquilo (C_1-C_6); R_3 es -CO_2H, -$CONH_2$, -CONHOH, -$CONHSO_2R_7$, tetrazol, -SO_2NHR_7, -SO_3H, -$PO(OH)NH_2$, -$PO(OH)OR_7$, -$CONHR_7$, -$COOR_7$, un grupo de ácido mimético, o un heterocicloalquilo de 5 o 6 miembros o heteroarilo que contiene 1 a 4 heteroátomos seleccionados de O, N, S; R_4 es -CO_2H, -$CONH_2$, -(CH2)nOR_7, o -$CONR_9R_{10}$

TRADUCCIÓN OFICIAL N° 0901081 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

Traducción de Declaración Juramentada (Affidávit) relacionada con cesión a WYETH de invención titulada:

"**INHIBIDORES DE AGRECANASA GLUTAMATO.**"

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:

   BARBARA A. KIELY
3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY
4. LLEVA EL SELLO DE BARBARA A. KIELY, NOTARIO

CERTIFICADO

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

5. EN TRENTON, NUEVA JERSEY
6. EL 8 DE AGOSTO DE 2007
7. POR: Bradley Abelow, TESORERO DE NUEVA JERSEY
8. N° A299607
9. SELLO (APARECE ADHERIDO SELLO DORADO)
10. FIRMA (FIRMADO) BRADLEY ABELOW

AM102063 L1

DECLARACIÓN JURAMENTADA

Yo, Michelle L. McGowan, Asociado de Legalizaciones de Wyeth, por medio del presente certifico que la copia anexa ha sido comparada con la Cesión original (para USSN 60/697.590 y cualquier equivalente legal de la misma en un país

extranjero, para la invención titulada: "INHIBIDORES DE AGRECANASA GLUTAMATO.") de fecha agosto 8, 2005 de Jerauld Stanley Skotnicki y de fecha agosto 11, 2005 de Phaik-Eng Sum, David Brian How y Joshua James Sabatini y de fecha agosto 18, 2005 de Tarek Suhayl Mansour y de fecha agosto 25, 2005 de Jason Shaoyun Xiang, Manus Ipek, Steve Yik-Kai Tam y Eric Feyfant a Wyeth y que la mencionada copia es una copia auténtica del original.

Fechado hoy 6 de agosto de 2007 en Madison, Nueva Jersey, Estados Unidos de América.

Wyeth
(Firmado)
Michelle L. McGowan
Asociado de Legalizaciones

PARA SER USADO EN COLOMBIA

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Dec 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

RECONOCIMIENTO

Estado de Nueva Jersey)
)
Condado de Morris)

Hoy 6 de agosto de 2007, compareció personalmente ante mí Michelle L. McGowan, Asociado de Legalizaciones de Wyeth, a quien conozco comó la persona describa en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en forma libre y espontánea para los fines consignados en él.

(Firmado) Barbara A. Kiely, Notario Público
(Sello en tinta que dice: "Barbara A. Kiely ID. 33893, Notario Público de Nueva Jersey. Mi comisión vence el 20 de junio de 2009")

TRADUCCIÓN OFICIAL N° 0901081 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

(Sello notarial realzado)

[Aparece en el encabezamiento de las páginas referentes a la cesión:
"Archivo No. 36119.191 US1 (AM102063)
Patente
(Aparece en el pie de página de las páginas referentes a la cesión:
"Cesión de Invención; Solicitud Provisional")

Cesión de Invención

En consideración del pago por la CESIONARIA al CEDENTE de una contraprestación válida y suficiente cuyo recibo se acusa por medio del presente, el CEDENTE:

(1) Nombre Completo del Inventor: Phaik-Eng SUM
Residencia: 16 Chamberlain Court, Pomona NY 10970
Ciudadanía: Canadá

(2) Nombre Completo del Inventor: David Brian HOW
Residencia: 10 High Avenue, Nyack NY 10960
Ciudadanía: Canadá

JAIME A. GARAVITO B
TRADUCTOR E INTÉRPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

(3) Nombre Completo del Inventor: Joshua James SABATINI
Residencia: 3 Old Mamaroneck Rd., Apt. 5E, White Plains NY 10606
Ciudadanía: Estados Unidos de América

(4) Nombre Completo del Inventor: Jerauld Stanley SKOTNICKI
Residencia: 148 Gallows Hill Road, Westfield NJ 07090
Ciudadanía: Estados Unidos de América

(5) Nombre Completo del Inventor: Tarek Suhayl MANSOUR
Residencia: 5 Overlook Road, New City NY 10956
Ciudadanía: Canadá

(6) Nombre Completo del Inventor: Jason Shaoyun XIANG
Residencia: 3 River Street, Winchester MA 01890
Ciudadanía: Estados Unidos de América

(7) Nombre Completo del Inventor: Manus IPEK
Residencia: 197 School Street, Watertown MA 02472
Ciudadanía: Estados Unidos de América

(8) Nombre Completo del Inventor: Steve Yik-Kai TAM

TRADUCCIÓN OFICIAL N° 0901081 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

Residencia: 88 Woodside Avenue, Wellesley MA 02482
Ciudadanía: Estados Unidos de América

(9) Nombre Completo del Inventor: Eric FEYFANT
Residencia: 41 Kendell Road, Lexington MA 02421
Ciudadanía: Francia

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

por medio del presente vende, cede y transfiere a la CESIONARIA:

Wyeth
Five Giralda Farms
Madison, New Jersey 07940

y los sucesores, CESIONARIOS y representantes legales de la CESIONARIA, la totalidad del derecho, título e intereses para los Estados Unidos y sus posesiones territoriales y en todos los países extranjeros, incluyendo todos los derechos a reivindicar prioridad con respecto a la invención titulada:

INHIBIDORES DE AGRECANASA GLUTAMATO

e inventada por el CEDENTE y los siguientes inventores adicionales, si los hubiere:

y que se encuentra en la Solicitud Provisional de los EE.UU. No. 60/697.590 presentada el 11 de julio de 2005.

[También verificar si se están cediendo solicitud(es) extranjera(s)]

[X] y cualquier equivalente legal de la(s) misma(s) en un país extranjero

la fecha de presentación y número de solicitud de la mencionada solicitud de los Estados Unidos debe insertarse cuando se conozca, incluyendo el derecho a invocar prioridad, incluyendo todas y cada una de las mejoras divulgadas en la

misma y en todas las patentes obtenidas para dicha invención a través de la anterior solicitud y cualquier solicitud provisional, no provisional, continuación, divisional, renovación o sustitución de la misma presentada posteriormente y en cuanto a la patente, cualquier re-expedición o nuevo examen de la misma.

Los CEDENTES por medio del presente acuerdan que no se ha hecho ni se hará o suscribirá ninguna cesión, venta, acuerdo o gravamen que pueda estar en conflicto con esta cesión.

Los CEDENTES autorizan a la CESIONARIA para que haga solicitudes y para que reciban patentes para dicha invención en cualquiera de los mencionados países en su propio nombre, o en el nombre de la CEDENTE o a su elección.

Los CEDENTES acuerdan suscribir u obtener cualquier seguridad adicional necesaria del título a dicha invención y cualquier patente que pueda ser expedida para la misma y a entregar en cualquier momento y a solicitud y expensas de la CESIONARIA cualquier testimonio en cualquier derecho preexistente que impida el patentamiento de la invención, litigio o procedimiento relacionado y a suscribir todos los documentos que puedan ser necesarios o convenientes para perfeccionar el título a dicho invento o cualquier patente que pueda ser otorgada para el mismo a la CESIONARIA, sus sucesores, CESIONARIOS u otros representantes legales y a suscribir, en cualquier momento, a solicitud y expensas de la CESIONARIA, cualquier continuación, continuación parcial, divisional, renovación o sustitución de la misma y en cuanto a patentes a re-expedir o re-examinar las mismas, o cualesquier otras solicitudes adicionales de patentes para dicho invento o cualquier parte del mismo, todas

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

las cuales y cualquier patente que se expida se ceden por medio del presente a la CESIONARIA y prestará todos los juramentos legales o declaraciones y hará todos los actos legales requeridos para adquirirlos, sin compensación adicional, pero a expensas de la CESIONARIA, sus sucesores, cesionarios u otros representantes legales.

Los CEDENTES autorizan y solicitan al Comisionado de Patentes expedir todas y cada una de las patentes de los Estados Unidos para dicho invento, que resulte de cualquiera de las solicitudes a su CESIONARIA.

(Firmado)
Phaik-Eng SUM

Agosto 11, 2005
Fecha

JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

RECONOCIMIENTO

Estado de Nueva York)
Declaración juramentada:
Condado de Rockland)

El 11 de agosto de 2005, Phaik-Eng SUM, compareció personalmente ante mí, quien presentó prueba satisfactoria de identificación, y a quien conozco como la persona describa en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en forma libre y espontánea para los fines consignados en él.

[Firmado] Rose Ann D. Jastrow

[Sello en tinta que dice: "ROSEANN D. JASTROW. No. 01JA6085816. Calificado en el Condado de Rockland. Mi comisión vence el 06 de enero de 2007"]

TRADUCCIÓN OFICIAL N° 0901081 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

---

(Firma ilegible) Agosto 11, 2005
David Brian HOW Fecha

RECONOCIMIENTO

Estado de Nueva York)
Declaración juramentada:
Condado de Rockland)

El 11 de agosto de 2005, David Brian HOW, compareció personalmente ante mí, quien presentó prueba satisfactoria de identificación, y a quien conozco como la persona describa en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en forma libre y espontánea para los fines consignados en él.

[Firmado] Rose Ann D. Jastrow

[Sello en tinta que dice: "ROSEANN D. JASTROW. No. 01JA6085816. Calificado en el Condado de Rockland. Mi comisión vence el 06 de enero de 2007"]

(Firmado) Agosto 11, 2005
Joshua James SABATINI Fecha

RECONOCIMIENTO

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

Estado de Nueva York)
Declaración juramentada:
Condado de Rockland)

El 11 de agosto de 2005, Joshua James SABATINI, compareció personalmente ante mí, quien presentó prueba satisfactoria de identificación, y a quien conozco como la persona describa en el anterior instrumento y quien suscribió el mismo y

reconoció haberlo suscrito en forma libre y espontánea para los fines consignados en él.

[Firmado] Rose Ann D. Jastrow

[Sello en tinta que dice: "ROSEANN D. JASTROW. No. 01JA6085816. Calificado en el Condado de Rockland. Mi comisión vence el 06 de enero de 2007"]

(Firmado) Agosto 8, 2005
Jerauld Stanley SKOTNICKI Fecha

RECONOCIMIENTO

Estado de Nueva York)
Declaración juramentada:
Condado de Rockland)

El 8 de agosto de 2005, Jerauld Stanley SKOTNICKI, compareció personalmente ante mí, quien presentó prueba satisfactoria de identificación, y a quien conozco como la persona describa en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en forma libre y espontánea para los fines consignados en él.

[Firmado] Janice A. White, Notario Público

[Sello en tinta que dice: "Janice A. White. Notario Público. Estado de Nueva York. N° 01-WH6052604. Calificado en el Condado de Rockland. Mi comisión vence el 26 de diciembre de 2006"]

(Firmado) Agosto 18, 2005
Tarek Suhayl MANSOUR Fecha

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Dec. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

TRADUCCIÓN OFICIAL N° 0901081 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

RECONOCIMIENTO

Estado de Nueva York)
Declaración juramentada:
Condado de Rockland)

El 18 de agosto de 2005, Tarek Suhayl MANSOUR, compareció personalmente ante mí, quien presentó prueba satisfactoria de identificación, y a quien conozco como la persona describa en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en forma libre y espontánea para los fines consignados en él.

[Firmado] Rose Ann D. Jastrow

[Sello en tinta que dice: "ROSEANN D. JASTROW. No. 01JA6085816. Calificado en el Condado de Rockland. Mi comisión vence el 06 de enero de 2007"]

(Firmado)
Jason Shaoyun XIANG

Agosto 25, 2005
Fecha

RECONOCIMIENTO

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

Estado de Massachusetts)
Declaración juramentada:
Condado de Middlesex)

El 25 de agosto de 2005, Jason Shaoyun XIANG, compareció personalmente ante mí, quien presentó prueba satisfactoria de identificación, a saber su licencia de conducción de Massachusetts y a quien conozco como la persona describa en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en mi presencia.

TRADUCCIÓN OFICIAL N° 0901081 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

[Firmado] Geraldine R. Gomes, Notario Público

[Sello que dice: "Geraldine R. Gomes. Notario Público. Estado de Massachusetts. Mi comisión vence el 18 de mayo de 2012"]

(Firmado) Manus IPEK — Agosto 25, 2005 Fecha

RECONOCIMIENTO

Estado de Massachusetts)
Condado de Middlesex) Declaración juramentada:

El 25 de agosto de 2005, Manus IPEK, compareció personalmente ante mí, quien presentó prueba satisfactoria de identificación, a saber su licencia de conducción de Massachusetts y a quien conozco como la persona describa en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en mi presencia.

[Firmado] Geraldine R. Gomes, Notario Público

[Sello que dice: "Geraldine R. Gomes. Notario Público. Estado de Massachusetts. Mi comisión vence el 18 de mayo de 2012"]

(Firmado) Steve Yik-Kai TAM — Agosto 25, 2005 Fecha

RECONOCIMIENTO

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

Estado de Massachusetts)
Condado de Middlesex) Declaración juramentada:

TRADUCCIÓN OFICIAL N° 0901081 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

El 25 de agosto de 2005, Steve Yik-Kai TAM, compareció personalmente ante mí, quien presentó prueba satisfactoria de identificación, a saber su licencia de conducción de Massachusetts y a quien conozco como la persona describa en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en mi presencia.

[Firmado] Geraldine R. Gomes, Notario Público

[Sello que dice: "Geraldine R. Gomes. Notario Público. Estado de Massachusetts. Mi comisión vence el 18 de mayo de 2012"]

(Firma ilegible)
Eric FEYFANT

Agosto 25, 2005
Fecha

RECONOCIMIENTO

JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

Estado de Massachusetts)
Declaración juramentada:
Condado de Middlesex)

El 25 de agosto de 2005, Eric FEYFANT, compareció personalmente ante mí, quien presentó prueba satisfactoria de identificación, a saber su licencia de conducción de Massachusetts y a quien conozco como la persona describa en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en mi presencia.

[Firmado] Geraldine R. Gomes, Notario Público

[Sello que dice: "Geraldine R. Gomes. Notario Público. Estado de Massachusetts. Mi comisión vence el 18 de mayo de 2012"]

TRADUCCIÓN OFICIAL N° 0901081 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

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La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 99792

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
BARBARA A KIELY

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
BARBARA A KIELY, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

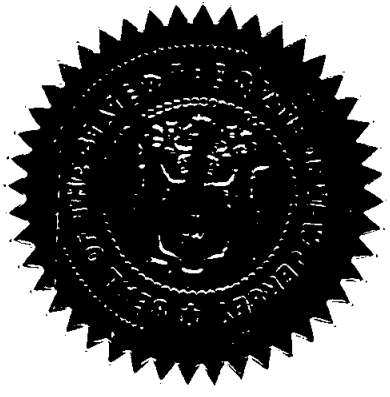
6. THE 8TH DAY OF AUGUST 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A299607

9. SEAL/STAMP:

10. SIGNATURE



Bradley Abelow

AM102063 L1

AFFIDAVIT

I, Michelle L. McGowan, Legalization Associate, Wyeth, do hereby certify that the attached copy has been compared with the original Assignment (for U.S.S.N. 60/697,590, and any legal equivalent thereof in a foreign country, for the invention entitled: "GLUTAMATE AGGRECANASE INHIBITORS") dated August 8, 2005 from Jerauld Stanley Skotnicki and dated August 11, 2005 from Phaik-Eng Sum, David Brian How, and Joshua James Sabatini and dated August 18, 2005 from Tarek Suhayl Mansour and dated August 25, 2005 from Jason Shaoyun Xiang, Manus Ipek, Steve Yik-Kai Tam, and Eric Feyfant to Wyeth and that the said copy is a true copy of the original.

Dated this 6th day of August, 2007, at Madison, New Jersey, United States of America.

Wyeth

Michelle L. McGowan
Legalization Associate

TO BE USED IN COLUMBIA

ACKNOWLEDGMENT

State of New Jersey)
)
County of Morris)

On this 6th day of August, 2007, before me personally appeared Michelle L. McGowan, Legalization Associate of Wyeth, to me known and known to me to be the individual described in and who executed the foregoing instrument, and she acknowledged to me that she executed the same.

Notary Public

Barbara A. Kiely ID. 33893
Notary Public of New Jersey
My Commission Expires June 20, 2009

Assignment of Invention

In consideration of the payment by ASSIGNEE to ASSIGNOR of good and valuable consideration, the receipt of which is hereby acknowledged,
ASSIGNOR:

(1) Full Name of Inventor: Phaik-Eng SUM
Residence: 16 Chamberlain Court, Pomona NY 10970
Citizenship: Canada

---

(2) Full Name of Inventor: David Brian HOW
Residence: 10 High Avenue, Nyack NY 10960
Citizenship: Canada

---

(3) Full Name of Inventor: Joshua James SABATINI
Residence: 3 Old Mamaroneck Rd., Apt. 5E, White Plains NY 10606
Citizenship: United States of America

---

(4) Full Name of Inventor: Jerauld Stanley SKOTNICKI
Residence: 148 Gallows Hill Road, Westfield NJ 07090
Citizenship: United States of America

---

(5) Full Name of Inventor: Tarek Suhayl MANSOUR
Residence: 5 Overlook Road, New City NY 10956
Citizenship: Canada

---

(6) Full Name of Inventor: Jason Shaoyun XIANG
Residence: 3 River Street, Winchester MA 01890
Citizenship: United States of America

---

(7) Full Name of Inventor: Manus IPEK
Residence: 197 School Street, Watertown MA 02472
Citizenship: United States of America

---

(8) Full Name of Inventor: Steve Yik-Kai TAM
Residence: 88 Woodside Avenue, Wellesley MA 02482
Citizenship: United States of America

---

(9) Full Name of Inventor: Eric FEYFANT
Residence: 41 Kendell Road, Lexington MA 02421
Citizenship: France

---

hereby sells, assigns and transfers to ASSIGNEE:

Wyeth
Five Giralda Farms
Madison, NJ 07940

and the successors, assigns and legal representatives of the ASSIGNEE the entire right, title and interest for the United States and its territorial possessions and in all foreign countries, including all rights to claim priority, in and to the invention entitled:
Glutamate Aggrecanase Inhibitors

and invented by ASSIGNOR and the following additional inventors, if any:

and which is found in U.S. Provisional Application No. 60/697,590 filed on: July 11, 2005

[also check if foreign application(s) is(are) also being assigned]

☒ and any legal equivalent thereof in a foreign country,

the date of filing and application number of said U.S. application when known, to be inserted above, including the right to claim priority, including any and all improvements disclosed therein, and in and to all Letters Patent to be obtained for said invention by the above application or any subsequently filed provisional, nonprovisional, continuation, divisional, renewal, or substitute thereof, and as to Letters Patent any reissue or re-examination thereof.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

ASSIGNOR authorizes ASSIGNEE to make applications for and to receive Letters patent for said invention in any of said countries in its own name, or in ASSIGNOR's name, at its election.

ASSIGNOR covenants and agrees to execute or procure any further necessary assurance of the title to said invention and any Letters Patent which may issue therefore and to, at any time, upon the request and at the expense of ASSIGNEE deliver any testimony in any interference, litigation or proceeding related thereto and execute all papers that may be necessary or desirable to perfect the title to said invention or any Letters Patent which may be granted therefore in ASSIGNEE, its successors, assigns or other legal representatives, and that to, at any time, upon the request and at the expense of ASSIGNEE execute any continuation, continuation-in-part, divisional, renewal or substitute thereof, and as to Letters Patent and reissue or re-examination thereof, or any other additional applications of Letters Patent for said invention or any part thereof, all of which applications and any Letters Patent issuing thereon are hereby assigned to ASSIGNEE, and will make all rightful oaths or declarations, and do all lawful acts requisite for procuring the same therein, without further compensation, but at the expense of ASSIGNEE, its successors, assigns or other legal representatives.

ASSIGNOR authorizes and requests the Commissioner of Patents to issue any and all Letters Patent of the United States for said invention, resulting from any of the aforesaid applications to its ASSIGNEE.

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Phaik Eng Sum — Aug 11, 05

Phaik-Eng SUM — Date

ACKNOWLEDGMENT

State of New York }
ss:
County of Rockland }

On the 11th day of August 2005, Phaik-Eng SUM personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

ROSEANN D. JASTROW
NO. 01JA6085816
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 01-06-2007

Rose Ann D. Jastrow
Notary Public

David Brian HOW — August 11, 2005

Date

ACKNOWLEDGMENT

State of New York }
ss:
County of Rockland }

On the 11th day of August 2005, David Brian HOW personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

ROSEANN D. JASTROW
NO. 01JA6085816
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 01-06-2007

Rose Ann D. Jastrow
Notary Public

Joshua James SABATINI

August 11, 2005
Date

ACKNOWLEDGMENT

State of New York }
ss:
County of Rockland }

On the 11th day of August 2005, Joshua James SABATINI personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

ROSEANN D. JASTROW
NO. 01JA6086816
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 01-06-2007

Roseann D. Jastrow
Notary Public

Jerauld Stanley SKOTNICKI

AUG 8, 2005
Date

ACKNOWLEDGMENT

State of New York }
ss:
County of Rockland }

On the 8 day of August 2005, Jerauld Stanley SKOTNICKI personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

JANICE A. WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO. 01-WH6052604
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-26-2006

Janice A. White
Notary Public

Tarek S. Mansour. — Aug 18, 05

Tarek Suhayl MANSOUR — Date

ACKNOWLEDGMENT

State of New York }
ss:
County of Rockland }

On the 18th day of August 2005, Tarek Suhayl MANSOUR personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

ROSEANN D. JASTROW
NO. 01JA6085816
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 01-06-2007

Rose Ann D. Jastrow
Notary Public

Jason Shaoyun Xiang — Aug. 25, 2005

Jason Shaoyun XIANG — Date

ACKNOWLEDGMENT

State of Massachusetts }
ss:
County of Middlesex }

On the 25th day of August 2005, before me personally appeared Jason Shaoyun XIANG, and proved to me through satisfactory evidence of identification, which was MA Driver's License, to be the person whose name is signed on the preceding or attached document in my presence.

GERALDINE R. GOMES
Notary Public
Commonwealth of Massachusetts
My Commission Expires May 18, 2012

G. R. Gomes
Notary Public

775

Manus IPEK

8/25/2005
Date

ACKNOWLEDGMENT

State of Massachusetts }
ss:
County of Middlesex }

On the 25th day of August 2005, before me personally appeared Manus IPEK, and proved to me through satisfactory evidence of identification, which was MA Driver's License, to be the person whose name is signed on the preceding or attached document in my presence.

GERALDINE R. GOMES
Notary Public
Commonwealth of Massachusetts
My Commission Expires May 18, 2012

Notary Public

Steve Yik-Kai Tam

Aug 25, 2005
Date

Steve Yik-Kai TAM

ACKNOWLEDGMENT

State of Massachusetts }
ss:
County of Middlesex }

On the 25th day of August 2005, before me personally appeared Steve Yik-Kai TAM, and proved to me through satisfactory evidence of identification, which was _____, to be the person whose name is signed on the preceding or attached document in my presence.

GERALDINE R. GOMES
Notary Public
Commonwealth of Massachusetts
My Commission Expires May 18, 2012

Notary Public

476

Eric FEYFANT

Date 08/25/2005

ACKNOWLEDGMENT

State of Massachusetts }
ss:
County of Middlesex }

On the 25th day of August 2005, before me personally appeared Eric FEYFANT, and proved to me through satisfactory evidence of identification, which was MA Driver's License, to be the person whose name is signed on the preceding or attached document in my presence.

GERALDINE R. GOMES
Notary Public
Commonwealth of Massachusetts
My Commission Expires May 18, 2012

Notary Public