Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 07-46791

54. **TÍTULO** PREPARACION Y USO DE DERIVADOS DE ACIDO BIFENIL -4-IL-CARBONILAMINO PARA EL TRATAMIENTO DE OBESIDAD

51. **CLASIFICACIÓN INTERNACIONAL** A61K31/03 //A61P3/04. A61k31/425

71. **SOLICITANTE** BAYER PHARMACEUTICALS CORPORATION

DOMICILIO CONNECTICUT, ESTADOS UNIDOS DE AMERICA

74. **APODERADO** EMILIO FERRERO
C.C. 438.019 de Usaquén

22. **BOGOTÁ, D. C.,** 10/05/2007

FN 15-05-2007
Publicada

(FORMA P-10)

SS

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
[redacted]
No. 07-046791- -00000-0000
Fecha: 2007-05-10 16:55:18 Dep: 2020 NUECREACIONES
Tra. 11 PATENTE(YI Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 344

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

SOLICITUD DE:

1. ☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
   ☐ Capítulo I. ☒ Capítulo II.

2. SOLICITANTE (71)

Nombre: **BAYER PHARMACEUTICALS CORPORATION**
sociedad constituida y existente bajo las leyes del Estado de Delaware, Estados Unidos de América.

Dirección: 400 Morgan Lane,
West Haven,
Connecticut 06516,
Estados Unidos de América

Domicilio: West Haven,
Connecticut,
Estados Unidos de América

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

3. REPRESENTANTE O APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@carnyp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

4. INVENTOR (ES) (72)

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   Estados Unidos de América
8. **Christiana AKUCHE**
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   Estados Unidos de América
9. **Tatiana SHELEKHIN**
   4 High Valley Road,
   Ridgefield,
   Connecticut 06877,
   Estados Unidos de América

5 **PCT (86)**
Solicitud Internacional No. PCT/US2005/037215 Fecha: 14 de octubre de 2005
Publicación Internacional No. WO 2006/044775 A3 Fecha: 27 de abril de 2006

6 TÍTULO (54)
PREPARACIÓN Y USO DE DERIVADOS DE ÁCIDO BIFENIL-4-IL-CARBONILAMINO PARA EL TRATAMIENTO DE OBESIDAD.

7 **Clasificación Internacional (51)** C07D 277/82 A61K31/03 // A61K31/425 A61P3/04

8

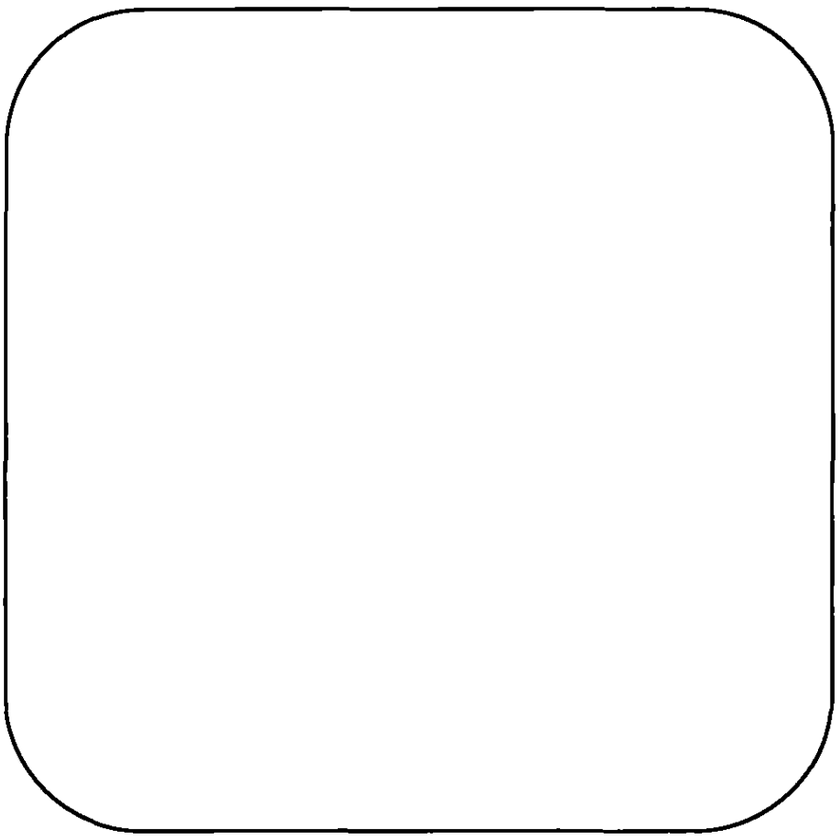
Prioridad SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	15 de octubre de 2004	60/618.975

9 **Comprobante de pago No.:** 07-23.290 **Fecha:** 21 de marzo de 2007

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 482.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☒ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

(11) **FIGURA CARACTERÍSTICA**



(12) Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

NNJ

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2006/044775 A3

   Descripción:

   Páginas 103 en el idioma original

   Páginas 164 en español

   Reivindicaciones: Número (s) 32

   Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ Extracto de publicación.

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 – COLOMBIA

181

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of-Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER-OF-ATT RNEY

14125
5829

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

BAYER PHARMACEUTICALS CORPORATION

domiciliado (s) en/of 400 Morgan Lane
West Haven, CT 06516
United States of America

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23535 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4a N° 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare finitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades 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 patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela,

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4a N° 72□35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the corresponding certificate shall suffice. If any of the appointees were to die, the following alternate shall take his place. When the absence or impediment of the principal representative or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time. In addition, we grant a Power of Attorney in favor of the above□named attorneys□at□law so that they may obtain the protection of my (our) industrial property and against the unfair competition, 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 patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ

COMO NOTARIO PÚBLICO DEL CÍRCULO
FOTOCOPIA COINCIDE CON EL ORIGINAL
04 ABR 2002
PABLO MENDEZ BARAJAS
NOTARIO (E)

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: The United States of America

THIS PUBLIC DOCUMENT

2. has been signed by **ELAINE PORTER**

3. acting in the capacity of **NOTARY PUBLIC**

4. in the State of Connecticut for the term of **July 1, 2001 to June 30, 2006**

CERTIFIED

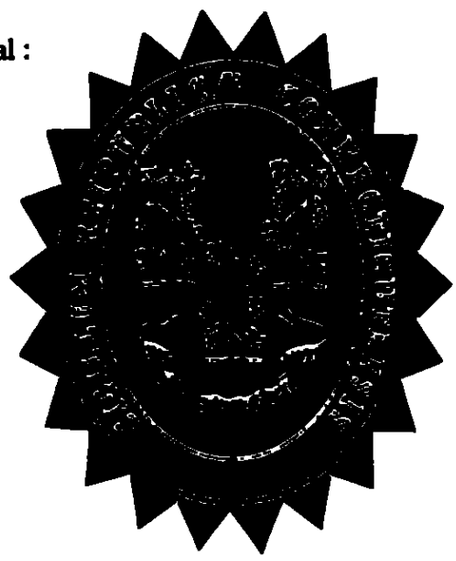
5. at Hartford, Connecticut

6. on **February 5, 2004**

7. by **SUSAN BYSIEWICZ** Secretary of the State of Connecticut

8. Number : **2004-1177**

9. Seal :



COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

04 ABR 2007

PABLO MENDEZ BARAJAS
NOTARIO (E)

10. Signature

Susan Bysiewicz

Secretary of the State

ia protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso□administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

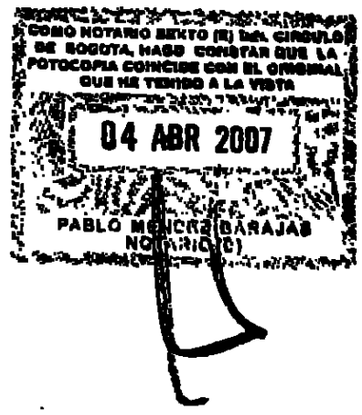
Dado y firmado hoy/Given and signed this 30 January 2004

en/in West Haven, Connecticut, United States of America

por/by Jeffrey M. Greenman

Assistant Secretary of Bayer Pharmaceuticals Corporation

Firma/Signature



— NOTARIO PÚBLICO O FUNCIONARIO AUTORIZADO — NOTARY PUBLIC OR ATTESTING OFICIAL —

CERTIFICACIÓN NOTARIAL (SOCIEDAD)

A los 30 días del mes de Enero de 2004 compareció(eron) ante mí, Jeffrey M. Greenman Secretario Assistente de Bayer Pharmaceuticals Corporation

Quien(es) conozco personalmente y que firma(n) este documento en representación de la Sociedad/compañía denominada Bayer Pharmaceuticals Corporation

Certifico:

1. Que he visto los siguientes documentos:*
1. Certificado de Constitucion de Bayer Pharmaceuticals Corporation fechado 14 Nov. 2002;
2. Resolucion de la Junta Directiva fechado 1 Enero, 2003
3. Consentimiento escrito de fundador Único de Bayer Pharmaceuticals Corporation fechado 14 Noviembre 2002, eligiendo la Junta Directiva

2. Que dichos documentos prueban lo siguiente:

2.1. Que Bayer Pharmaceuticals Corporation es una Sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes de l Estado de Delaware Estados Unidos de America

2.2. Que el domicilio de dicha Sociedad/Compañía es 400 Morgan Lane,-West Haven, Connecticut 06516, Estados Unidos de America

2.3. Que el objeto u objetos para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad/Compañía.

2.4. Que el(los) Sr.(Sres.) Jeffrey M. Greenman está(n) autorizado(s) para otorgar el presente Poder.

Ciudad West Haven

Estado Connecticut, Estados Unidos de America

Hoy 30 Enero de 2004

NOTARIAL CERTIFICATION (CORPORATION)

On this 30th day of January 200 4 appeared before me *Jeffrey M. Greenman*

Assistant Secretary of Bayer Pharmaceuticals Corporation

who(m) I know personally and who(m) signed this document as representative(s) of the Corporation/Company named *Bayer Pharmaceuticals Corporation*

I certify:

1. That I have seen the following documents:*

1) Certificate of Incorporation of Bayer Pharmaceuticals Corporation dated 14 November 2002;
2) Resolution of the Board of Directors dated 1 January 2003;
3) Written Consent of the Sole Incorporator of Bayer Pharmaceuticals Corporation dated 14 November 2002 electing the Board of Directors;

2. That the above documents duly prove the following:

2.1. That *Bayer Pharmaceuticals Corporation* is a Corporation/Company legally constituted and in existence in accordance with the laws *of the State of Delaware, United States of America*

2.2. That the domicile of said Corporation/Company is *400 Morgan Lane, West Haven, Connecticut 06516 United States of America*

2.3. That the purpose or purposes for which the present Power of Attorney is granted are comprised within the corporation purposes set forth in the charter of the mentioned Corporation/Company.

2.4. That Mr.(Messrs.) *Jeffrey M. Greenman* is(are) authorized to grant the present Power of Attorney

City *West Haven*

State *Connecticut, United States of America*

This *30th* day of *January* 200 *4*

By: .....
Paul R. Berry
Vice President, General Counsel and Secretary
of Bayer Pharmaceuticals Corporation

COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA.... 30 ENE 2007 PABLO MENDEZ BARRIOS NOTARIO (6)

NOTARIAL CERTIFICATE

United States of America
State of Connecticut
County of New Haven
City of West Haven

On this the 30th day of the month of January 2004, before me, Notary Public practicing in this locality, appeared Paul R. Berry, known to me to be the person whose name is subscribed to the foregoing instrument, who acknowledged himself to be Vice President, General Counsel and Secretary of Bayer Pharmaceuticals Corporation, and that acting in such capacity and with authorization, he executed the foregoing instrument on behalf of Bayer Pharmaceuticals Corporation for the purposes therein contained.

In witness thereof I set my hand.

NOTARY PUBLIC
My Commission Expires

[NOTARIAL SEAL]

Elaine Porter
Notary Public
My Commission Expires June 30, 2008

TRADUCCIÓN OFICIAL 031/2004 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL **BAYER PHARMACEUTICALS CORPORATION** EMPRESA DOMICILIADA EN **400 MORGAN LANE, WEST HAVEN, CT 06516, ESTADOS UNIDOS DE AMÉRICA** OTORGA PODER A EMILIO FERRERO, TPA 31929, GONZALO PERDOMO, TPA 831; LUZ CLEMENCIA DE PAEZ TPA 23555 Y A GERMÁN CAVELIER, TPA 832. EXPEDIDO Y FIRMADO EL 30 DE ENERO DE 2004 EN WEST HAVEN, CONNECTICUT, ESTADOS UNIDOS DE AMÉRICA POR JEFFREY M. GREENMAN, SUBSECRETARIO DE BAYER PHARMACEUTICALS CORPORATION. FIRMA:(ILEGIBLE)

CERTIFICADO NOTARIAL EN INGLES Y EN ESPAÑOL DE FECHA 30 DE ENERO DE 2004 POR EL CUAL SE CERTIFICA LA COMPARECENCIA DE JEFFREY M GREENMAN A NOMBRE DE BAYER PHARMACEUTICALS CORPORATION Y PARA CERTIFICAR LA EXISTENCIA LEGAL, EL DOMICILIO DE DICHA EMPRESA Y LA CAPACIDAD DE M. GREENMAN PARA COMPROMETER A DICHA FIRMA. WEST HAVEN, CONNECTICUT, ESTADOS UNIDOS DE AMÉRICA, 30 DE ENERO DE 2004.

POR: FIRMADO: PAUL R. BERRY, VICE PRESIDENTE, ASUNTOS JURÍDICOS Y SECRETARIO DE BAYER PHARMACEUTICALS CORPORATION.

CERTIFICADO NOTARIAL

ESTADOS UNIDOS DE AMÉRICA

ESTADO DE CONNECTICUT, CONDADO DE NEW HAVEN

CIUDAD DE WEST HAVEN

10

Hoy 30 de enero de 2004, ante mí, notario público practicante en esta localidad, compareció Paul R. Berry, conocido mío como la persona cuyo nombre aparece escrito en el documento precedente, y quien reconoció ser el vicepresidente, jefe de asuntos jurídicos y secretario de Bayer Pharmaceuticals Corporation y que actuando en calidad de tal y con autorización, firmó el documento precedente a nombre de Bayer Pharmaceuticals Corporation para los objetivos allí contenidos. En testimonio de lo anterior, firmo: ELAINE PORTER, notario público. Sello: ELAINE PORTER, notario público. Mi cargo vence el 30 de junio de 2006.

APOSTILLA:

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

1. Estados Unidos de América

Este documento público

2. ha sido firmado por ELAINE PORTER

3. quien actúa en su calidad de NOTARIO PÚBLICO

4. del estado de Connecticut para el período entre el primero de julio de 2001 y el 30 de junio de 2006

CERTIFICADO

5. en Hartford, Connecticut

6. el 5 de febrero de 2004

7. por Susan Bysiewicz Secretario del estado de Connecticut

8. Número 2004-1177

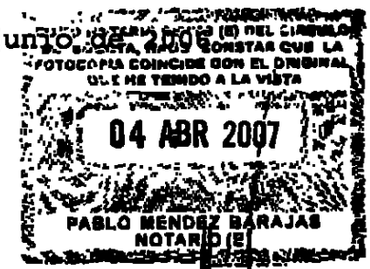
9. Sello:

El sello del estado de Connecticut

10. Firma: Susan Bysiewicz, secretario de estado.

COLO-14125-841-001-0; WPCL002G. ID 5326

Bogotá, 16 de febrero de 2004.



Eduardo Cabello N.
Eduardo Cabello Noguera
TRADUCTOR OFICIAL
Res. 541 Febrero de 1994

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S)

CONCUERDA CON LA FIRMA REGISTRADA POR
(LOS) EN ESTA NOTARIA
16 FEB. 2004

PABLO MENDEZ
BARAJAS

NO SE ANOTA
INSCRIBE EN EL TEXTO

16 FEB 04

JEFE GRUPO LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES
EXTERIORES

12914

DOCUMENTO DE IDENTIDAD
No.

NOTARIO SEXTO (6) DEL CIRCULO
BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE TENGO A LA VISTA
04 ABR 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application BAYER PHARMACEUTICALS CORPORATION is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from SMITH, Roger to BAYER PHARMACEUTICALS CORPORATION, dated 14 October 2005 (14.10.2005)
VIII-2-1(iv)		an assignment from O'CONNOR, Stephen, J. to BAYER PHARMACEUTICALS CORPORATION, dated 14 October 2005 (14.10.2005)
VIII-2-1(iv)		an assignment from COISH, Philip to BAYER PHARMACEUTICALS CORPORATION, dated 10 October 2005 (10.10.2005)
VIII-2-1(iv)		an assignment from LOWE, Derek to BAYER PHARMACEUTICALS CORPORATION, dated 11 October 2005 (11.10.2005)
VIII-2-1(iv)		an assignment from CLARK, Roger, B. to BAYER PHARMACEUTICALS CORPORATION, dated 11 October 2005 (11.10.2005)
VIII-2-1(iv)		an assignment from STEBBINS, Jeffrey to BAYER PHARMACEUTICALS CORPORATION, dated 14 October 2005 (14.10.2005)
VIII-2-1(iv)		an assignment from CAMPBELL, Ann-Marie to BAYER PHARMACEUTICALS CORPORATION, dated 13 October 2005 (13.10.2005)
VIII-2-1(iv)		an assignment from AKUCHE, Christiana to BAYER PHARMACEUTICALS CORPORATION, dated 14 October 2005 (14.10.2005)
VIII-2-1(iv)		an assignment from SHELEKHIN, Tatiana to BAYER PHARMACEUTICALS CORPORATION, dated 12 October 2005 (12.10.2005)
VIII-2-1(ix)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

12

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

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
27 April 2006 (27.04.2006)

(10) International Publication Number
WO 2006/044775 A3

(51) International Patent Classification:
C07D 277/82 (2006.01)

(21) International Application Number:
PCT/US2005/037215

(22) International Filing Date: 14 October 2005 (14.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/618,975 15 October 2004 (15.10.2004) US

(71) Applicant *(for all designated States except US)*: **BAYER PHARMACEUTICALS CORPORATION** [US/US]; 400 Morgan Lane, West Haven, Connecticut 06516 (US).

(72) Inventors; and

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(54) Title: PREPARATION AND USE OF BIPHENYL-4-YL-CARBONYLAMINO ACID DERIVATIVES FOR THE TREATMENT OF OBESITY

(57) Abstract: This invention relates to certain biphenyl-4-yl carbonylamino acid compounds, compositions, and methods for treating or preventing obesity and related diseases.

WO 2006/044775 A3

PREPARATION AND USE OF BIPHENYL-4-YL-CARBONYLAMINO ACID DERIVATIVES FOR THE TREATMENT OF OBESITY

[001] This application claims benefit of U.S. Provisional Application Serial No. 60/618,975; filed on October 15, 2004, the contents of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[002] This invention relates to certain biphenyl-4-yl carbonylamino acid compounds, compositions, and methods for treating or preventing obesity and related diseases.

BACKGROUND OF THE INVENTION

[003] Obesity, which is an excess of body fat relative to lean body mass, is a chronic disease that is highly prevalent in modern society. It is associated not only with a social stigma, but also with decreased life span and numerous medical problems, including adverse psychological development, coronary artery disease, hypertension, stroke, diabetes, hyperlipidemia, and some cancers (*see, e.g.*, Nishina, et al., Metab. 43:554-558, 1994; Grundy and Barnett, Dis. Mon. 36:641-731, 1990; Rissanen, et al., British Medical Journal, 301:835-837, 1990).

[004] Obesity remains a problem, and treatment has been limited. There is, therefore, a need to develop pharmaceuticals and treatment regimes effective in the alleviation of obesity.

[005] A hallmark characteristic of obesity is an increase in white adipose tissue (WAT) mass that is largely due to accumulation of triacylglycerol. This increase in WAT mass is a key contributor to obesity-associated complications. Diacylglycerol O-acyltransferases (DGATs, EC 2.3.1.2) are membrane-bound enzymes that catalyze the terminal step of triacylglycerol biosynthesis. Two enzymes that display DGAT activity have been characterized: DGAT-1 (diacylglycerol O-acyltransferase type 1) (*see, e.g.*, U.S. Patent No. 6,100,077; Cases, et al., Proc. Nat. Acad. Sci. 95:13018-13023, 1998) and DGAT-2 (diacylglycerol O-acyltransferase type 2) (Cases, et al., J. Biol. Chem. 276:38870-38876, 2001). DGAT-1 and DGAT-2 do not exhibit significant protein sequence identity. Importantly, DGAT-1 null mice do not become obese when challenged with a high fat diet in contrast to wild-type littermates (Smith, et al., Nature Genetics 25:87-90, 2000). DGAT-1 null mice display reduced postprandial plasma glucose levels and exhibit increased energy expenditure, but have normal levels of serum triglycerides (Smith, et al., 2000), possibly due to the preserved DGAT-2 activity. Since DGAT-1 is expressed in the intestine and adipose tissue (Cases, et al., 1998), there are at least two possible mechanisms to explain the resistance of DGAT-1 null mice to diet-induced obesity. First, abolishing DGAT-1 activity in the intestine may block the reformation and export of triacylglycerol from intestinal cells into the circulation via chylomicron particles. Second, knocking out DGAT-1 activity in the adipocyte may decrease deposition of triacylglycerol in WAT.

The phenotype of the DGAT-1 null mouse, along with the results of our studies with DGAT-1 inhibitors in diet-induced obese (DIO) mice, indicate that a DGAT-1 inhibitor has utility for the treatment of obesity and obesity-associated complications.

SUMMARY OF THE INVENTION

[006] The present invention relates to biphenyl-4-yl carbonylamino acid compounds, compositions, and methods for the treatment and prevention of obesity and related diseases.

[007] Accordingly, one embodiment of the present invention is to provide compounds as depicted in the Tables and in the Examples.

[008] Another embodiment of the invention is to provide a method of treating or preventing obesity and related diseases in a subject comprising administering to a subject in need thereof an effective amount of at least one compound of the invention.

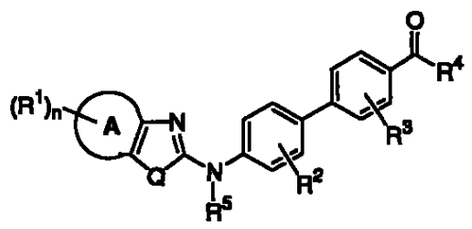
[009] A further embodiment of the present invention is to provide compositions for treating or preventing obesity and related diseases in a subject comprising an effective amount of at least one compound of the invention.

[010] These and other objects of the invention will be clear in light of the detailed description below.

DETAILED DESCRIPTION OF THE INVENTION

[011] The invention relates to biphenyl-4-yl carbonylamino acid derivatives, and pharmaceutical salts and esters thereof, that have utility in the inhibition of DGAT-1 (diacylglycerol O-acyltransferase type 1) and in the treatment of obesity and related diseases.

[012] One embodiment of the invention is a compound of Formula (I)



(I)

wherein

Q is O, NR^{11}, or S;



is a fused ring selected from

an aromatic 6-membered ring containing 0 or 1 N atoms;

R^1 is independently selected from

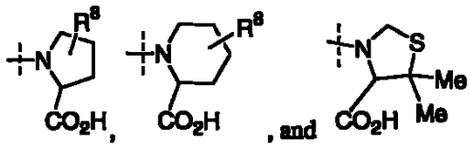
halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, cyano, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, aminocarbonyl, (C_1-C_6)alkylaminocarbonyl, bis[(C_1-C_6)alkyl]aminocarbonyl, aminosulfonyl, (C_1-C_6)alkylaminosulfonyl, bis[(C_1-C_6)alkyl]aminosulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl,

and

when two of said R^1 substituents are (C_1-C_6)alkyl and are attached to adjacent carbon atoms of the Ring A, they may be joined together to form a 5-7-membered carbocyclic ring;

n is 0, 1, or 2;

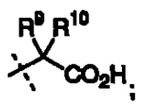
R^2 and R^3 are independently selected from hydrogen, halo, hydroxy, (C_1-C_6)alkyl, trifluoromethyl, (C_1-C_6)alkoxy, and trifluoromethoxy;

R^4 is selected from 

wherein

R^6 is H or CH_3;

and

R^7 is  ;

wherein

R^9 is selected from

(C_1-C_6)alkyl optionally substituted with one or two groups selected from vinyl, CF_3, OH, methoxy, SCH_3, NH_2, -CO_2H, and -$CONH_2$,

$(CH_2)_m$phenyl wherein m is 0 to 3, and

where the phenyl ring is optionally substituted with one or two groups selected from halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, OH, nitro, and cyano,

piperidinyl optionally substituted on C with halo and optionally substituted on C or N with (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, or cyano,

tetrahydropyran-4-yl;

R^{10} is H or methyl;

or

R^9 and R^{10} may form, together with the carbon to which they are attached, a 3- to 6-membered carbocyclic ring,

R^8 is hydrogen, (C_1-C_4)alkyl, hydroxy, or methoxy;

R^5 is selected from H, (C_1-C_6)alkyl, and hydroxy-(C_2-C_6)alkyl;

R^{11} is selected from H, (C_1-C_6)alkyl, and hydroxy-(C_2-C_6)alkyl;

and the pharmaceutically acceptable salts and esters thereof.

[013] The terms identified above have the following meaning throughout:

[014] The term "halo" means F, Br, Cl, and I.

[015] The terms "(C_1-C_4)alkyl," "(C_1-C_6)alkyl," and "(C_2-C_6)alkyl" mean a linear or branched saturated hydrocarbon groups having from 1 to about 4 carbon atoms, from 1 to about 6 carbon atoms, or from 2 to about 6 carbon atoms, respectively. The hydrocarbon group may also include a cyclic alkyl fragment as part of the alkyl group. Such groups include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, cyclopropyl, cyclohexyl, cyclopropyl-methyl, and cyclopentyl-methyl groups.

[016] The term "(C_1-C_6)alkoxy" means a linear or branched saturated hydrocarbon group having from 1 to about 6 carbon atoms, said group being attached to an oxygen atom. The oxygen atom is the atom through which the alkoxy substituent is attached to the rest of the molecule. The hydrocarbon group may also include a cyclic alkyl fragment as part of the alkyl group. Such groups

include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *n*-hexyloxy, 3,3-dimethylpropoxy, cyclopropoxy, cyclopropylmethoxy, cyclopentyloxy, and the like.

[017] The term "(C_1-C_6)haloalkoxy" means a (C_1-C_6)alkoxy group substituted on carbon with a halogen atom. Such groups include, for example, trifluoromethoxy, difluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 3-fluoropropoxy, 2-chloroethoxy, 3-chloropropoxy, 1-fluoro-2,2,-dichloroethoxy, and the like.

[018] The term "(C_1-C_6)haloalkyl" means a (C_1-C_6)alkyl group substituted on carbon with a halogen atom. Such groups include, for example, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, difluoroethyl, 1-fluoro-2,2-dichloroethyl, 3-chloropropyl, 4-bromohexyl, and the like.

[019] The terms "aminocarbonyl," "(C_1-C_6)alkylaminocarbonyl," and "bis[(C_1-C_6)alkyl]aminocarbonyl" mean a carbonyl [C(=O)] group substituted by nitrogen atom in which the nitrogen atom is unsubstituted, substituted by a single (C_1-C_6)alkyl group, or by two (C_1-C_6)alkyl groups, respectively. The carbonyl group is the point of attachment of the substituent to the rest of the molecule. Such groups include, for example, carboxamido [$NH_2C(=O)$-], *N*-methylcarboxamido [$CH_3NHC(=O)$], *N*-methyl-*N*-propylcarboxamido [$CH_3CH_2CH_2N(CH_3)C(=O)$-], *N,N*-diethylcarboxamido [$(CH_3CH_2)_2NC(=O)$-], and the like.

[020] The terms "3- to 6-membered carbocyclic ring" and "5- to 7-membered carbocyclic ring" mean a saturated or partially unsaturated ring containing from about 3 to about 6 carbon atoms, and from about 5 to about 7 carbon atoms, respectively. Such groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, and the like.

[021] The term "hydroxy-(C_2-C_6)alkyl" means a (C_2-C_6)alkyl group, said alkyl being further substituted by a hydroxy group at any available carbon atom. Such groups include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2 hydroxypropyl, 3 hydroxypropyl, 4-hydroxybutyl, 2-hydroxy-1-methylethyl, 5-hydroxypentyl, 3-hydroxybutyl, 3-hydroxy-2-ethylpropyl, 6-hydroxyhexyl, and the like.

[022] The term "hydroxy-(C_2-C_6)alkylaminocarbonyl" means a carbonyl [C(=O)] group substituted by nitrogen atom in which the nitrogen atom is substituted by a single (C_2-C_6)alkyl group, and said alkyl is further substituted by a hydroxy group. Such groups include, for example, 2-hydroxyethylamido-, 3-hydroxypropylamido, 4-hydroxyhexylamido, and the like.

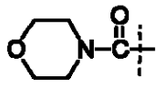
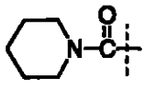
[023] The terms "aminosulfonyl," "(C_1-C_6)alkylaminosulfonyl," and "bis[(C_1-C_6)alkyl]aminosulfonyl" mean a $S(=O)_2$ group substituted by nitrogen atom in which the nitrogen

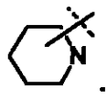
atom is unsubstituted, substituted by a single (C_1-C_6)alkyl group, or by two (C_1-C_6)alkyl groups, respectively. The $S(=O)_2$ group is the point of attachment of the substituent to the rest of the molecule. Such groups include, for example, aminosulfonyl [$NH_2S(=O)_2$-], *N*-methylaminosulfonyl-[$CH_3NHS(=O)_2$], *N*-methyl-*N*-propylaminosulfonyl [$CH_3CH_2CH_2N(CH_3)S(=O)_2$-], *N,N*,-diethylaminosulfonyl [$(CH_3CH_2)_2NS(=O)_2$-], and the like.

[024] The term "(C_1-C_6)alkylcarbonylamino" means an amino group in which the nitrogen atom is substituted by a carbonyl group, and said carbonyl group is further substituted by a (C_1-C_6)alkyl group. The nitrogen atom is the point of attachment of the substituent to the rest of the molecule. Such groups include, for example, acetylamino [$CH_3C(=O)NH$-], propanoylamino [$CH_3CH_2C(=O)NH$-], *i*-butanoylamino [$(CH_3)_2CHC(=O)NH$-] groups, and the like.

[025] The term "(C_1-C_6)alkylsulfonylamino" means an amino group in which the nitrogen atom is substituted by a sulfonyl [$S(=O)_2$] group, and said sulfonyl group is further substituted by a (C_1-C_6)alkyl group. The nitrogen atom is the point of attachment of the substituent to the rest of the molecule. Such groups include, for example, methylsulfonylamino [$CH_3S(=O)_2NH$-], propylsulfonylamino [$CH_3CH_2CH_2S(=O)_2NH$-], *i*-propylsulfonylamino [$(CH_3)_2CHS(=O)_2NH$-] groups, and the like.

[026] The terms "1-morpholinylcarbonyl" and "1-piperidinylcarbonyl" mean

 and  , respectively.

[027] The term "piperidinyl" means  . The point of attachment of this substituent may be either the N or any C atom in the ring.

[028] The term "optionally substituted" means that the moiety so modified may have from none to up to at least the highest number of substituents indicated. Each substituent may replace any hydrogen atom on the moiety so modified as long as the replacement is chemically possible and chemically stable. When there are two or more substituents on any moiety, each substituent is chosen independently of any other substituent and can, accordingly, be the same or different.

[029] Standard amino acid fragment abbreviations (e.g., Val, Leu, Ile, Pro, and the like) are used in the Tables below to describe a bivalent amino acid fragment. It is to be understood that the attachment points of the bivalent fragment are through the nitrogen atom of the fragment and the carbon atom of the carbonyl group. For example, in Table 1a, the fragment is attached to the molecule through the nitrogen atom and is substituted on the C(=O) with an OH group. As entered

into the Table, the attachment point to the rest of the molecule is on the left, and the OH group is on the right. It also to be understood that when the fragment is designated as "L," its absolute configuration is that of the naturally occurring amino acids; whereas the designation "D" is of the opposite absolute configuration.

[030] The compounds described in the Examples are intended to be representative of the invention, and it will be understood that the scope of the invention is not limited by the scope of the examples. Those skilled in the art will recognize that the invention may be practiced with variations on the disclosed structures, materials, compositions and methods, and such variations are regarded as within the ambit of the invention.

[031] Representative salts of the compounds of Formula (I) include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, and undecanoate.

[032] Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine salts and *N*-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides, and iodides; aralkyl halides like benzyl and phenethyl bromides and others.

[033] The esters in the present invention are non-toxic, pharmaceutically acceptable ester derivatives of the compounds of Formula (I). This may include, for example, ester derivatives prepared from acetic, benzoic, mandelic, stearic, lactic, salicylic, hydroxynaphthoic, glucoheptonic, and gluconic acid. The compounds of Formula (I) may be esterified by a variety of conventional procedures well known by those skilled in the art. For example, esterification may be reached using the appropriate carboxylic acid in the presence of trifluoroacetic anhydride and optionally, pyridine, or in the presence of *N,N*-carbonyldiimidazole with pyridine. One skilled in the art would readily know how to successfully carry out these as well as other methods of esterification. Sensitive or reactive

groups on the compound of Formula (I) may need to be protected during any of the above methods for forming esters, and protecting groups may be added and removed by conventional methods well known in the art.

[034] It will be appreciated that diastereomers and enantiomers of the exemplified structures will often be possible, and that pure isomers represent one embodiment of the invention. It is intended that pure stereoisomers, and mixtures thereof, are within the scope of the invention.

[035] The compounds of this invention may, either by nature of asymmetric centers or by restricted rotation, be present in the form of isomers. Any isomer may be present in the (*R*)-, (*S*)-, or (*R,S*) configuration, preferably in the (*R*)- or (*S*)- configuration, whichever is most active.

[036] All isomers, whether separated, pure, partially pure, or in racemic mixture, of the compounds of this invention are encompassed within the scope of this invention. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art.

[037] Geometric isomers by nature of substituents about a double bond or a ring may be present in cis (= *Z*-) or trans (= *E*-) form, and both isomeric forms are encompassed within the scope of this invention.

[038] The particular process to be utilized in the preparation of the compounds of this invention depends upon the specific compound desired. Such factors as the selection of the specific moieties and the specific substituents on the various moieties, all play a role in the path to be followed in the preparation of the specific compounds of this invention. These factors are readily recognized by one of ordinary skill in the art.

[039] For synthesis of any particular compound, one skilled in the art will recognize that the use of protecting groups may be required for the synthesis of compounds containing certain substituents. A description of suitable protecting groups and appropriate methods of adding and removing such groups may be found in the art (*see, e.g.*, T. W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis;* Wiley: New York, (1999)).

[040] In the reaction schemes below, one skilled in the art will recognize that reagents and solvents actually used may be selected from several reagents and solvents well known in the art to be effective equivalents. When specific reagents or solvents are shown in a reaction scheme, therefore, they are meant to be illustrative examples of conditions desirable for the execution of that particular reaction scheme. Abbreviations not identified in accompanying text are listed later in this disclosure under "Abbreviations and Acronyms."

[041] Another object of this invention is to provide methods of making the compounds of the invention. The compounds may be prepared from readily available materials by the methods outlined in the Reaction Schemes and Examples below, and by obvious modifications thereto.

General Preparation of Compounds of the Invention

[042] Preparation of the biphenyl-4-yl-carbonylamino acid derivatives of the present invention, having Formula (I), may be accomplished by the Methods and Reaction Schemes described below. Methods for the preparation of specific compounds having Formula (II), (III), (IV), (VI), (XI), (XII), and (XIII) are also described in the experimental procedures that follow below.

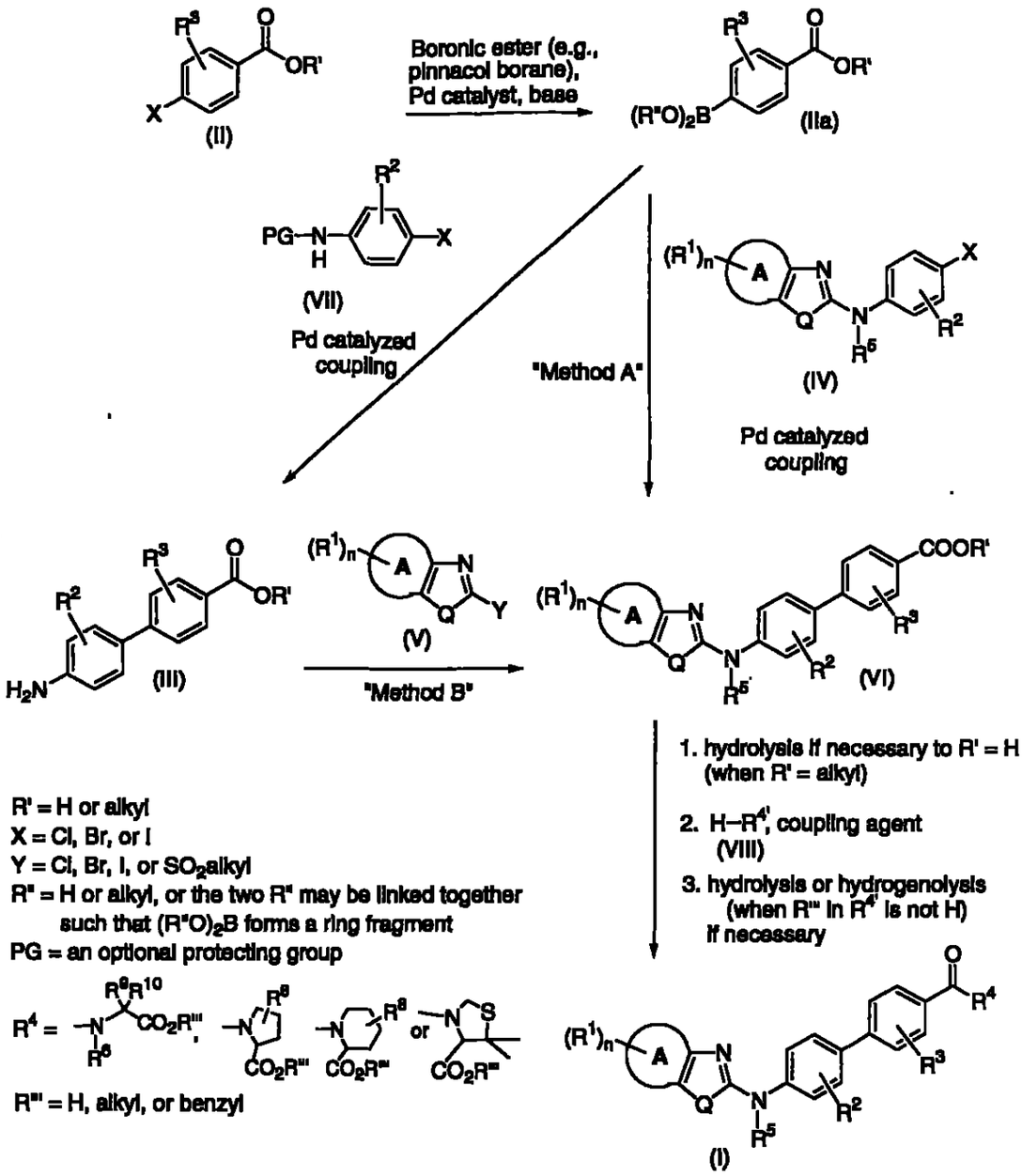
[043] Compounds of Formula (V) wherein 'A' is a benzo moiety may be prepared by the methods described in PCT/US04/14036 and by other methods known in the art, such as the following: (a) 2-chloro-5-cyanobenzothiazole and 2-chloro-6-cyanobenzothiazole (WO 2002/000633); (b) 5-acetamido-2-chlorobenzothiazole (Sharpe, et al., J. Med. Chem. 15:523-529, 1972); (c) 6-acetamido-2-chlorobenzothiazole (Katz, J. Am. Chem. Soc. 73:4007-4010, 1951); (d) 2-chloro-5-benzothiazole-carboxamide, 2-chloro-*N*-methyl-6-benzothiazolecarboxamide, 2-chloro-*N*-ethyl-5-benzothiazole-carboxamide, 2-chloro-*N,N*-dimethyl-5-benzothiazolecarboxamide, 2-chloro-*N,N*-dimethyl-6-benzo-thiazolecarboxamide, 2-chloro-*N*-(2-hydroxyethyl)-5-benzothiazolecarboxamide, 2-chloro-*N*-(2-hydroxyethyl)-6-benzothiazolecarboxamide, and 2-chloro-7-morpholinocarbonyl-benzothiazole (U.S. Patent No. 3,654,296); (è) 6-butoxy-2-chloro-benzothiazole (Bordi, et al., Farmaco 49:153-166, 1994); (f) 2-chloro-6-isopropoxy-benzothiazole, 2-chloro-5-cyano-benzoxazole, and 5-cyano-2-methylthiobenzothiazole (Eur. Patent Appl. EP1308439A1); (g) 2-chloro-5-methylsulfonyl-benzoxazole (Lok, et al., J. Org. Chem. 61:3289-3297, 1996); (h) 2-chloro-5-cyanobenzoxazole (Eur. Pat. Appl. EP1308439A1). Compounds of Formula (V) wherein 'A' is a heteroaryl moiety such as a pyrido or pyrimido moiety may be prepared by methods known in the art, such as described for the following compounds and intermediates related to Formula (V): (a) 2-chloro[1,3]thiazolo[4,5-b]pyridine (Viviani, et al., Bull. Soc. Chim. Fr. 130:395-404, 1993); (b) 2-chloro-5-methyl[1,3]thiazolo[4,5-b]pyridine (U.S. Patent No. 5,496,816); (c) [1,3]thiazolo[5,4-b]pyridine-2-thiol (U.S. Patent No. 5,077,287); (d) [1,3]thiazolo[5,4-c]pyridine-2-thiol and [1,3]thiazolo[4,5-c]pyridine-2-thiol (WO 2003/039258); and (e) 6-chloro[1,3]thiazolo[4,5-b]pyridine-2-thiol (WO 2003/006470).

[044] Unless otherwise specified, Q, A, and R^1-R^{11} have the identical meanings as described above.

[045]

Reaction Scheme 1

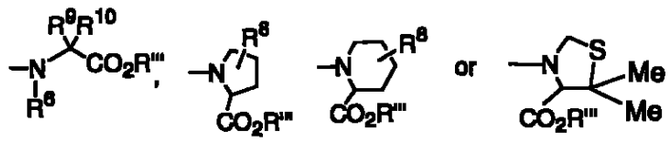
Methods A and B



[046] In Reaction Scheme 1, a boronic ester derivative of Formula (IIa) is prepared by reaction of the compound of Formula (II), where X = halo, a Pd catalyst, and a boronic ester (e.g., pinnacol borane). The compound of Formula (VI) may then be prepared by "Method A" by coupling the compound of Formula (IIa), with the compound of Formula (IV) in the presence of a palladium catalyst and a base such as potassium carbonate (Suzuki conditions).

[047] Alternatively, the Formula (IIa) compound may be coupled with an aniline of Formula (VII), also under Suzuki conditions, to provide the biphenyl compound of Formula (III). The compound of Formula (VI) may then be prepared by Method B, by reaction of the Formula (III) compound with the compound of Formula (V), in the optional presence of a acid catalyst (e.g., HCl).

[048] Further reaction of the compound of Formula (VI), where R' is H, with an amino acid derivative of Formula (VIII), where $R^{4'}$ is

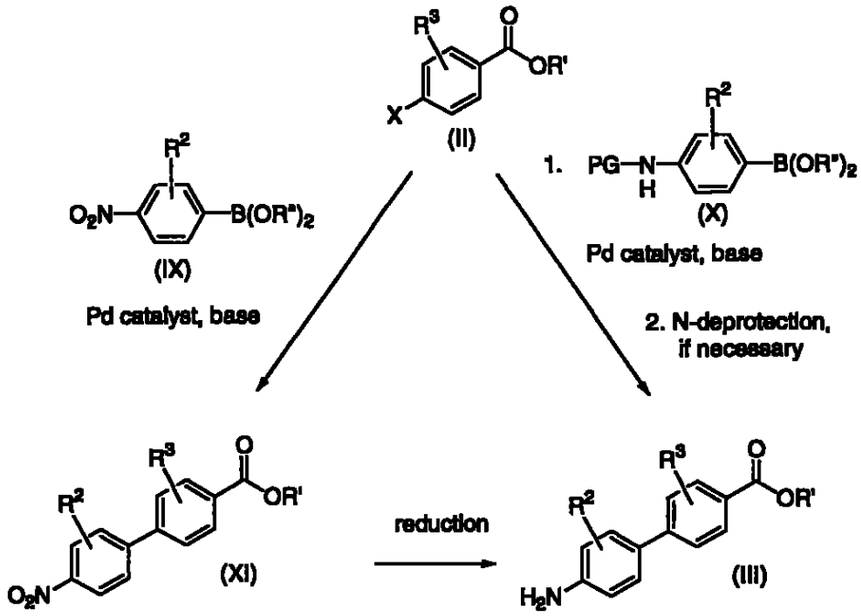


in the optional presence of a coupling agent such as *N,N'*-diisopropylcarbodiimide, provides an intermediate that is either hydrolyzed (where R''' is alkyl) under basic conditions such as LiOH, THF, and water, or hydrogenated (where R''' is benzyl) using H_2 and a suitable catalyst, to give the invention compound of Formula (I).

[049] The intermediate of Formula (III), used in Method B, may also be prepared by the alternative methods outlined in Reaction Scheme 2.

[050] **Reaction Scheme 2**

Alternate Methods for the Preparation of (III)



R' = H or alkyl
X = Cl, Br, or I
R" = H or alkyl, or the two R" may be linked together such that $(R"O)_2B$ forms a ring fragment
PG = an optional protecting group

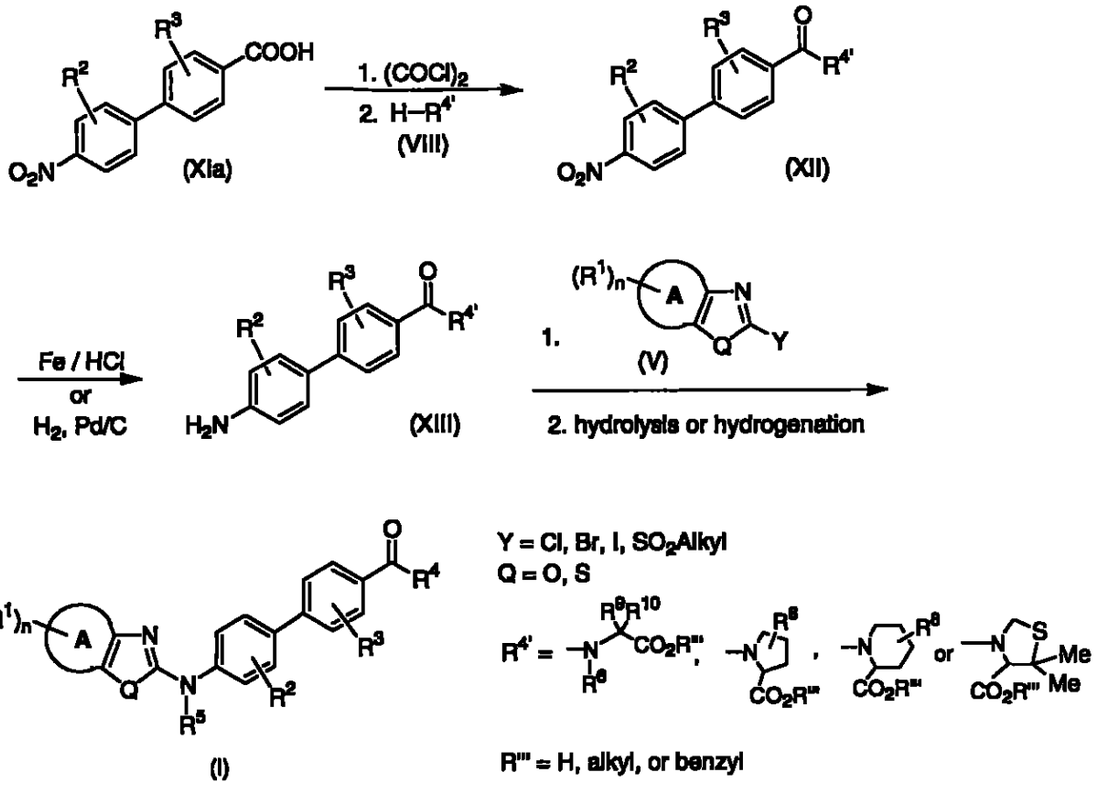
[051] For example, the compound of Formula (II) may be coupled with a nitrophenylboronic acid derivative of Formula (IX) under Suzuki conditions (Pd catalyst and base) to give the compound of Formula (XI). Reduction of the Formula (XI) intermediate (e.g., H_2 Pd/C or Fe/HCl) gives the aminobiphenyl compound Formula (III). Alternatively, the Formula (II) compound may be coupled with a protected aminoboronic acid derivative of Formula (X), to give, following removal of the protecting group, the intermediate of Formula (III).

[052] Preparation of the Formula (I) compounds may also be accomplished by Method C, as illustrated in Reaction Scheme 3.

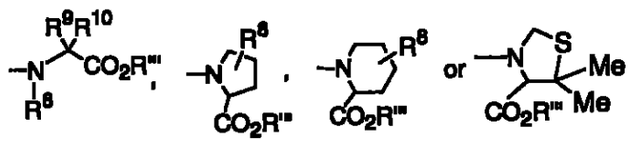
[053]

Reaction Scheme 3

Method C



[054] In this route, a nitrobiphenyl compound of Formula (XIa) is converted to the Formula (XII) compound by conversion of (XIa) to the corresponding acid chloride (e.g., using $(COCl)_2$) followed by coupling with the amino acid derivative of Formula (VIII), where $R^{4'}$ is

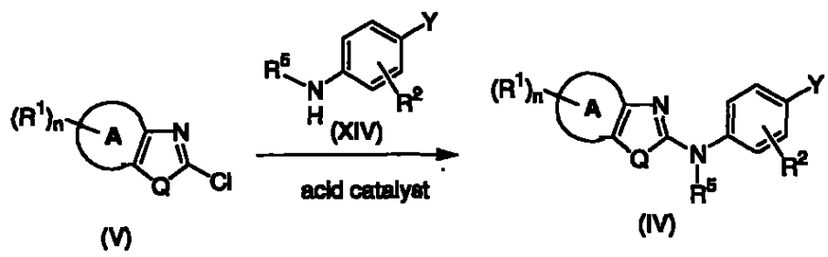


in the optional presence of a base. Alternatively, the compound of Formula (XII) can be prepared by reacting (XIa) and (VIII) in the presence of a coupling agent such as dicyclohexylcarbodiimide or other standard coupling agents. The nitro group in the compound of Formula (XII) is then reduced with, for example, H_2 and Pd/C or Fe/HCl, to produce the intermediate compound of Formula (XIII). Reaction of (XIII) with the compound of Formula (V) in the presence of an acid catalyst (e.g., HCl) followed by hydrolysis or hydrogenation as in Reaction Scheme 1, gives the invention compound of Formula (I).

[055] Compounds of Formula (IV) are prepared as illustrated in Reaction Scheme 4, by reaction of

an aniline of Formula (XIV) with the intermediate of Formula (V), for example, under acid conditions (e.g., HCl in *n*-butanol) at 90°C.

[056] **Reaction Scheme 4**



Y = Cl, Br, I, or SO_2alkyl

[057] Specific embodiments of the invention may be found in the Examples described below and in Tables 1-7. The compounds described in these Examples and Tables are intended to be representative of the invention, and it will be understood that the scope of the invention is not limited by the scope of the examples. Those skilled in the art will recognize that the invention may be practiced with variations on the disclosed structures, materials, compositions and methods, and such variations are regarded as within the ambit of the invention.

PREPARATION OF COMPOUNDS OF THE INVENTION

Mass spectra

[058] Chemical ionization mass spectra (CI-MS) were obtained with a Hewlett Packard 5989A mass spectrometer equipped with a Hewlett Packard 5890 Gas Chromatograph with a J & W DB-5 column (0.25 uM coating; 30 m x 0.25 mm). The ion source was maintained at 250°C and spectra were scanned from 50-800 amu at 2 sec per scan.

[059] Liquid chromatography – electrospray mass spectra (LC-MS) data were obtained by using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluants were A: 2% acetonitrile in water with 0.02% TFA, and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% B over 3.5 minutes at a flow rate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold of 0.5 minutes at 95% B. Total run time was 6.5 minutes. In the Examples and Tables provided below, the LC-MS data are given with HPLC retention times (ret. time).

NMR Spectra

[060] Routine one-dimensional NMR spectroscopy was performed on 300 MHz or 400 MHz Varian Mercury-plus spectrometers. The samples were dissolved in deuterated solvents obtained from Cambridge Isotope Labs, and transferred to 5 mm ID Wilmad NMR tubes. The spectra were acquired at 293°K. The chemical shifts were recorded on the ppm scale and were referenced to the appropriate solvent signals, such as 2.49 ppm for DMSO-d_6, 1.93 ppm for CD_3CN, 3.30 ppm for CD_3OD, 5.32 ppm for CD_2Cl_2, and 7.26 ppm for $CDCl_3$ for ^1H spectra; and 39.5 ppm for DMSO-d_6, 1.3 ppm for CD_3CN, 49.0 ppm for CD_3OD, 53.8 ppm for CD_2Cl_2 and 77.0 ppm for $CDCl_3$ for ^{13}C spectra.

Abbreviations and Acronyms

[061] When the following abbreviations are used throughout this disclosure, they have the following meaning:

Ala	alanine
Biotage®	medium-pressure silica gel chromatography, using apparatus from Biotage Inc./Dyax Corp.
$CDCl_3$	deuterated chloroform
Celite®	diatomaceous earth filter agent, obtained from Celite Corp.
DCE	dichloroethane
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI-MS	electron impact – mass spectroscopy
h	hour(s)
HPLC	high pressure liquid chromatography
Ile	isoleucine
LC-MS	liquid chromatography – mass spectroscopy
Leu	leucine
min	minutes
MS	mass spectroscopy
NMR	nuclear magnetic resonance
Phe	phenylalanine
p.o.	orally
Pro	proline
rt	room temperature

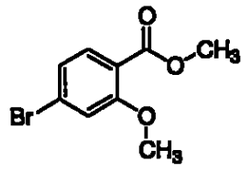
THF	tetrahydrofuran
TLC	thin layer chromatography
TFA	trifluoroacetic acid
Val	valine

[062] By using the described methods herein, the compounds of the invention may be prepared. The following examples are presented to further illustrate the invention described herein, but they should not be construed as limiting the scope of the invention in any way.

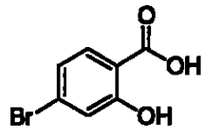
Preparation of Intermediates

Compounds of Formula (II)

[063] Intermediate II- 1: Methyl 4-bromo-2-methoxybenzoate

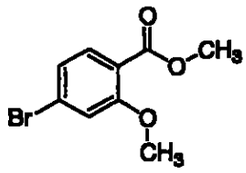


[064] Step 1. Preparation of 4-bromo-2-hydroxybenzoic acid



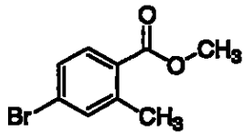
[065] t-Butyl nitrite (5.10 g, 49.5 mmol) was added to a suspension of copper(II) bromide (8.80 g, 39.4 mmol) in CH_3CN (50 mL), and the reaction mixture was cooled to 0°C in an ice bath. 4-Aminosalicylic acid (5.00 g, 32.7 mmol) was added in small portions over 30 min. Additional CH_3CN (20 mL) was added, and the reaction mixture was allowed to stir at 0°C for 2 h. The reaction mixture was poured into 20% HCl (200 mL) and extracted with Et_2O (2 x 200 mL). The combined organic phases were washed with 20% HCl (2 x 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in Et_2O (300 mL) and extracted with 15% NaOH (2 x 150 mL). The combined aqueous layers were washed with Et_2O (100 mL), brought to pH ~1 with 20% HCl, and extracted with Et_2O (3 x 200 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting solid was triturated with $CHCl_3$ and collected by filtration, yielding 2.5 g (35%) of the title compound as a crystalline solid. The material was used without further characterization or purification.

[066] Step 2. Preparation of methyl 4-bromo-2-methoxybenzoate



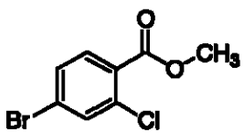
[067] 4-Bromo-2-hydroxybenzoic acid (1.00 g, 4.61 mmol) was dissolved in acetone (25 mL), and iodomethane (1.15 mL, 18.4 mmol) and K_2CO_3 (2.55 g, 18.4 mmol) were added. The reaction was heated at reflux overnight. Upon cooling to rt, the reaction mixture was filtered, and the filtrate was concentrated in vacuo. The crude material was purified by flash chromatography (Biotage® column; 10% EtOAc / Hexanes), yielding 0.955 g (85%) of the desired product as a yellow oil. *LC/MS m/z* 245.0 (MH^+); retention time 3.13 min. ^1H NMR (400 MHz, CD_2Cl_2) δ 3.84 (s, 3H), 3.90 (s, 3H), 7.12-7.20 (m, 2H), 7.62 (d, 1H).

[068] Intermediate II- 2: Methyl 4-bromo-2-methylbenzoate



[069] 4-Bromo-2-methylbenzoic acid (2.00 g, 9.30 mmol) was added to a solution of acetyl chloride (1.70 mL, 23.9 mmol) in methanol (30 mL). The mixture was allowed to stir at rt for 3 days and was then concentrated in vacuo. This gave 1.96 g (92%) of the title compound as a light brown oil. ^1H NMR (400 MHz, CD_2Cl_2) δ 2.61 (s, 3H), 3.90 (s, 3H), 7.38-7.42 (m, 2H), 7.78 (d, 1H).

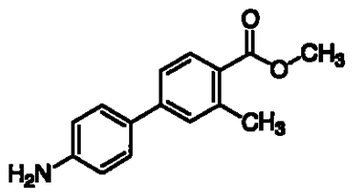
[070] Intermediate II- 3: Methyl 4-bromo-2-chlorobenzoate



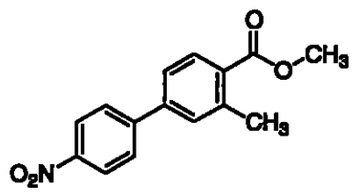
[071] 4-Bromo-2-chlorobenzoic acid (1.00 g, 4.25 mmol) was added to a solution of acetyl chloride (1.70 mL, 23.9 mmol) in methanol (30 mL). The mixture was allowed to stir at rt for 3 days, and was then concentrated in vacuo. This gave 0.84 g (80%) of the title compound. ^1H NMR (400 MHz, CD_2Cl_2) δ 3.85 (s, 3H), 7.51 (d, 1H), 7.45 (d, 1H), 7.78 (d, 1H).

Preparation of Intermediate Compounds of Formula (III)

[072] **Intermediate III- 1: Methyl 4'-amino-3-methylbiphenyl-4-carboxylate**

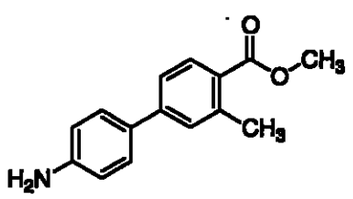


[073] Step 1. Preparation of methyl 3-methyl-4'-nitrobiphenyl-4-carboxylate



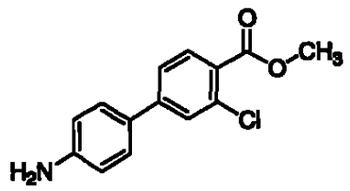
[074] To a solution of methyl 4-bromo-2-methylbenzoate (1.00 g, 4.37 mmol) and 4-nitrophenylboronic acid (2.91 g, 17.5 mmol) in toluene (12 mL) was added Na_2CO_3 (3.70 g, 34.9 mmol), 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) chloride complex with dichloromethane (0.71 g, 0.87 mmol), 1,4-dioxane (6 mL), and water (6 mL). The mixture was heated at reflux for 3 h and then allowed to cool to rt. The mixture was diluted with EtOAc and water, and the organic layer was isolated, dried over $MgSO_4$, and concentrated in vacuo. The material was purified by column chromatography (25% EtOAc in hexanes), yielding 1.32 g (89%) of the title compound. GC/MS *m/z* 271 (M^+); retention time 13.00 min. ^1H NMR (400 MHz, CD_2Cl_2) δ 2.65 (s, 3H), 3.95 (s, 3H), 7.52 (d, 2H), 7.78 (d, 2H), 8.11 (d, 1H), 8.30-8.39 (m, 2H).

[075] Step 2. Preparation of methyl 4'-amino-3-methylbiphenyl-4-carboxylate

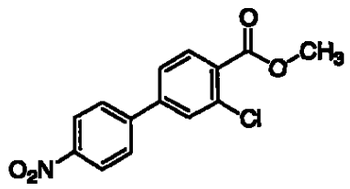


[076] Iron powder (1.04 g, 18.6 mmol) was added to a solution of methyl 3-methyl-4'-nitrobiphenyl-4-carboxylate (0.63 g, 1.9 mmol) in ethanol (20 mL). Concentrated HCl (0.93 mL, 1.9 mmol) was added, and the mixture was heated at reflux for 3 h. Upon cooling to rt, the mixture was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. The material was purified by column chromatography (33% EtOAc in hexanes), yielding 0.338 g (75%) of the title compound. LC/MS *m/z* 242.3 (MH^+); retention time 2.27 min. ^1H NMR (400 MHz, CD_2Cl_2) δ 2.81 (s, 3H), 3.95 (s, 3H), 6.83 (d, 2H), 7.41-7.51 (m, 4H), 7.85 (d, 1H).

[077] Intermediate III- 2: Methyl 4'-amino-3-chlorobiphenyl-4-carboxylate

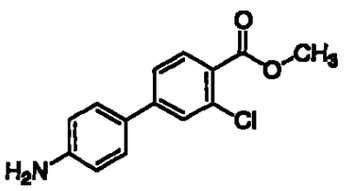


[078] Step 1. Preparation of methyl 3-chloro-4'-nitrobiphenyl-4-carboxylate



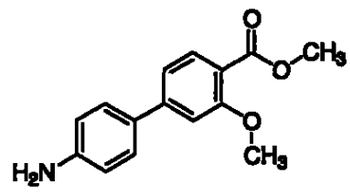
[079] To a solution of methyl 4-bromo-2-chlorobenzoate (0.40 g, 1.6 mmol) and 4-nitrophenylboronic acid (0.67 g, 4.0 mmol) in toluene (8 mL) was added Na_2CO_3 (1.02 g, 9.62 mmol), 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) chloride complex with dichloromethane (0.03 g, 0.03 mmol), 1,4-dioxane (4 mL), and water (4 mL). The mixture was heated at reflux for 3 h and then allowed to cool to rt. The mixture was diluted with EtOAc and water, and the organic layer was isolated, dried over $MgSO_4$, and concentrated in vacuo. The material was purified by column chromatography (25% EtOAc in hexanes), yielding 0.275 g (59%) of the title compound. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.98 (s, 3H), 7.58 (d, 2H), 7.68-7.82 (m, 3H), 7.97 (d, 1H), 8.33 (d, 1H).

[080] Step 2. Preparation of methyl 4'-amino-3-chlorobiphenyl-4-carboxylate

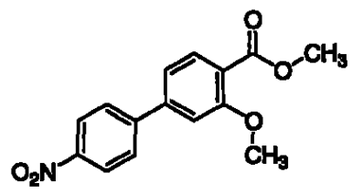


[081] Iron powder (0.99 g, 17.7 mmol) was added to a solution of methyl 3-chloro-4'-nitrobiphenyl-4-carboxylate (0.64 g, 1.8 mmol) in ethanol (15 mL). Concentrated HCl (0.88 mL, 1.8 mmol) was added, and the mixture was heated at reflux for 3 h. Upon cooling to rt, the mixture was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. The material was purified by column chromatography (33% EtOAc in hexanes), yielding 0.453 g (98%) of the title compound. LC/MS *m/z* 262.4 (MH^+); retention time 2.39 min. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.99 (s, 3H), 6.78 (d, 2H), 7.41-7.46 (m, 3H), 7.62 (s, 1H), 7.88 (d, 1H).

[082] Intermediate III- 3: Methyl 4'-amino-3-methoxybiphenyl-4-carboxylate

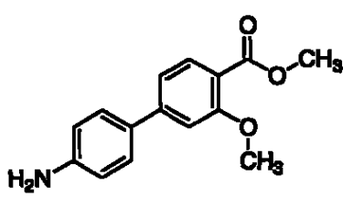


[083] Step 1. Preparation of methyl 3-methoxy-4'-nitrobiphenyl-4-carboxylate



[084] To a solution of methyl 4-bromo-2-methoxybenzoate (0.95 g, 3.9 mmol) and 4-nitrophenylboronic acid (1.29 g, 7.75 mmol) in toluene (10 mL) was added Na_2CO_3 (1.85 g, 17.4 mmol), 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) chloride complex with dichloromethane (0.06 g, 0.08 mmol), 1,4-dioxane (5 mL), and water (5 mL). The mixture was heated at reflux for 3 h and then allowed to cool to rt. The mixture was diluted with EtOAc and water, and the organic layer was isolated, dried over $MgSO_4$, and concentrated in vacuo. The material was purified by column chromatography (25% EtOAc in hexanes), yielding 0.675 g (61%) of the title compound. LC/MS *m/z* 287.9 (MH^+); retention time 3.14 min.

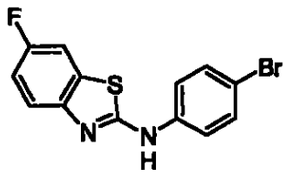
[085] Step 2. Preparation of methyl 4'-amino-3-methoxybiphenyl-4-carboxylate



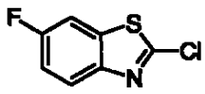
[086] Iron powder (0.58 g, 10 mmol) was added to a solution of methyl 3-methoxy-4'-nitrobiphenyl-4-carboxylate (0.38 g, 1.0 mmol) in ethanol (10 mL). Concentrated HCl (0.52 mL, 1.0 mmol) was added, and the mixture was heated at reflux for 3 h. Upon cooling to rt, the mixture was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. The material was purified by column chromatography (33% EtOAc in hexanes), yielding 0.279 g (quantitative yield) of the title compound. LC/MS *m/z* 258.3 (MH^+); retention time 1.65 min. ^1H NMR (400 MHz, CD_2Cl_2) δ 3.81 (s, 3H), 3.99 (s, 3H), 6.78 (d, 2H), 7.15-7.19 (m, 2H), 7.45 (d, 2H), 7.80 (d, 1H).

Preparation of Intermediate Compounds of Formula (IV)

[087] Intermediate IV-1: *N*-(4-bromophenyl)-6-fluoro-1,3-benzothiazol-2-amine

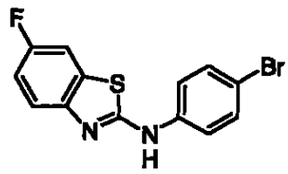


[088] Step 1. Preparation of 2-chloro-6-fluoro-benzothiazole



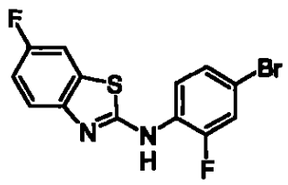
[089] 6-Fluoro-benzothiazole-2-thiol was treated with sulfuryl chloride by the procedure described in PCT/US04/14036 to give the desired product, which was used in the next step without further purification. EI-MS *m/z* 187 (M^+); ^{1}H NMR (DMSO-d_6) δ 8.00 (m, 2H), 7.40 (m, 1H).

[090] Step 2. Preparation of *N*-(4-bromophenyl)-6-fluoro-1,3-benzothiazol-2-amine



[091] A mixture of 2-chloro-6-fluoro-benzothiazole (0.65 g, 3.5 mmol) and 4-bromoaniline (0.61 g, 3.5 mmol) in n-butanol (6 mL) was heated at 60-70°C under nitrogen to obtain a solution, to which 4 M HCl in dioxane (0.43 mL, 1.73 mmol) was slowly added dropwise. The reaction mixture was then heated at 90°C for 18 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure. The resulting solid was triturated with ethanol and collected by filtration. This yielded 0.98 g (88%) of the title compound. LC/MS *m/z* 323.0 (MH^+); retention time 3.74 min. ^{1}H NMR (CD_3OD) δ 7.10-7.30 (m, 1H), 7.39 (d, 1H), 7.45 (d, 2H), 7.58-7.61 (m, 3H).

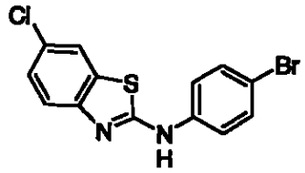
[092] Intermediate IV-2: *N*-(4-bromo-2-fluoro-phenyl)-6-fluoro-1,3-benzothiazol-2-amine



[093] In a similar manner to the procedure described above for the preparation of *N*-(4-bromophenyl)-6-fluoro-1,3-benzothiazol-2-amine, 2-chloro-6-fluoro-benzothiazole and 2-fluoro-4-

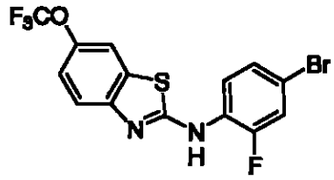
bromoaniline were reacted together to provide *N*-(4-bromo-2-fluoro-phenyl)-6-fluoro-1,3-benzothiazol-2-amine as a solid. ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.60 (t, 1H), 7.80 (d, 1H), 7.60 (m, 2H), 7.40 (d, 1H), 7.20 (m, 1H)).

[094] Intermediate IV-3: *N*-(4-bromophenyl)-6-chloro-1,3-benzothiazol-2-amine



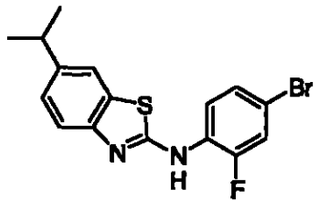
[095] A mixture of 2,6-dichlorobenzothiazole (0.71 g, 3.5 mmol) and 4-bromoaniline (0.61 g, 3.5 mmol) in n-butanol (6 mL) was heated at 60-70°C under nitrogen to obtain a solution, to which 4 M HCl in dioxane (0.43 mL, 1.73 mmol) was then slowly added dropwise. The reaction mixture was then heated at 90°C for 18 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure. The resulting solid was triturated with ethanol and collected by filtration. This yielded 1.09 g (93%) of the title compound. *LC/MS m/z* 339 (MH^+); retention time 3.98 min. ^{1}H NMR (CD_3OD) δ 7.31 (d, 1H), 7.42-7.58 (m, 5H), 7.61 (d, 1H).

[096] Intermediate IV-4: *N*-(4-bromo-2-fluorophenyl)-6-(trifluoromethoxy)-1,3-benzothiazol-2-amine



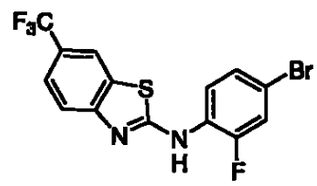
The preparation of this intermediate is described in US 2004/0224997.

[097] Intermediate IV-5: *N*-(4-bromo-2-fluorophenyl)-6-isopropyl-1,3-benzothiazol-2-amine



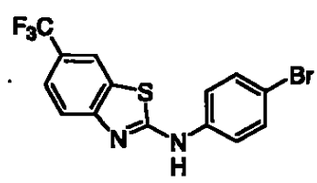
The preparation of this intermediate is described in US 2004/0224997.

[098] Intermediate IV-6: *N*-(4-bromo-2-fluorophenyl)-6-(trifluoromethyl)-1,3-benzothiazol-2-amine



The preparation of this intermediate is described in US 2004/0224997.

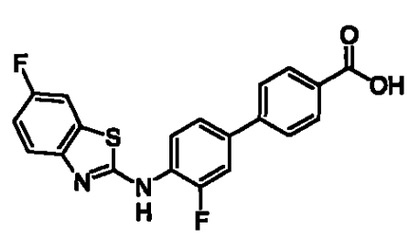
[099] Intermediate IV-7: *N*-(4-bromophenyl)-6-(trifluoromethyl)-1,3-benzothiazol-2-amine



This intermediate was prepared by the methods described in US 2004/0224997.

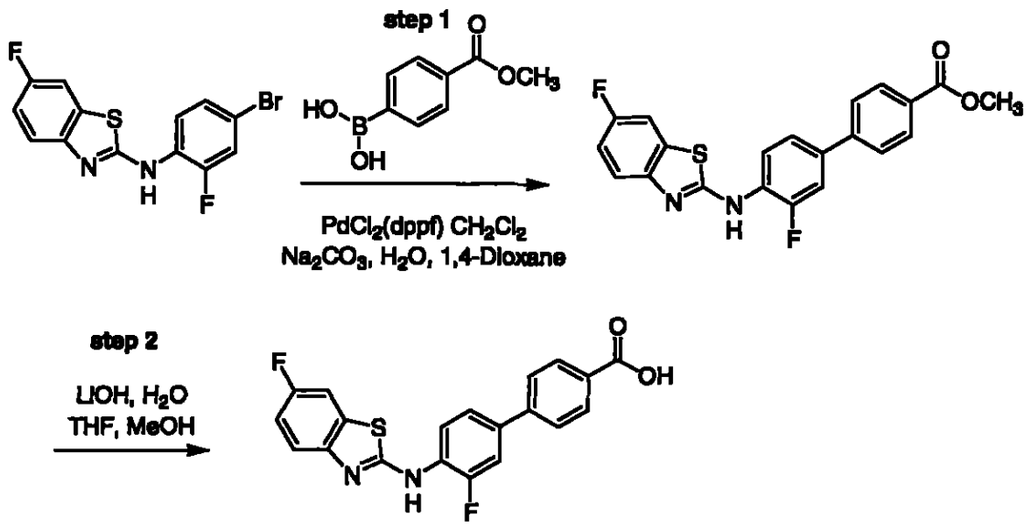
Preparation of Intermediate Compounds of Formula (VI) by Method A

[100] Intermediate VI-1: 3'-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylic acid

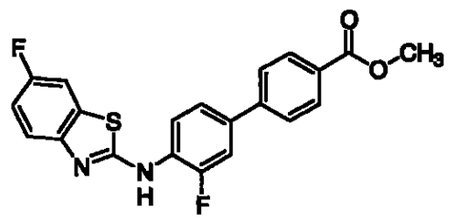


The preparation of 3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylic acid is described below in Reaction Scheme 5.

[101] **Reaction Scheme 5**

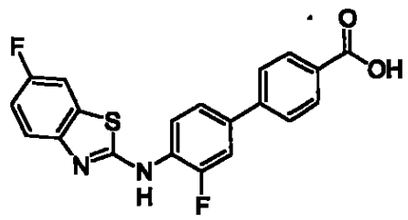


[102] Step 1. Preparation of methyl 3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylate



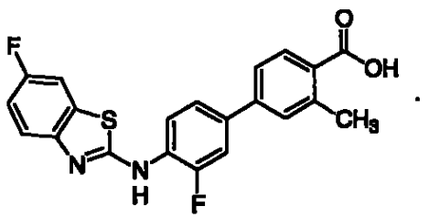
[103] As shown in Reaction Scheme 5, to a mixture of *N*-(4-bromo-2-fluorophenyl)-6-fluoro-1,3-benzothiazol-2-amine (1.00 g, 2.93 mmol) and 4-(methoxycarbonylphenyl)boronic acid (0.79 g, 4.40 mmol) in toluene (10 mL) was added Na_2CO_3 (1.40 g, 13.2 mmol), 1,1'-bis(diphenylphosphino) ferrocenepalladium(II) chloride complex with dichloromethane (0.05 g, 0.06 mmol), 1,4-dioxane (5 mL), and water (5 mL). This mixture was heated at reflux overnight. Upon cooling to rt, the reaction mixture was filtered, and the solid was washed with water (2 x 30 mL) and methanol (2 x 30 mL). The solid was recrystallized from acetone/MeOH (2:1). This yielded 0.641 g (55%) of the desired product as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82 (s, 3H), 7.20 (t, 1H), 7.59-8.02 (m, 8H), 8.70 (t, 1H), 10.50 (bs, 1H).

[104] Step 2. Preparation of 3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylic acid



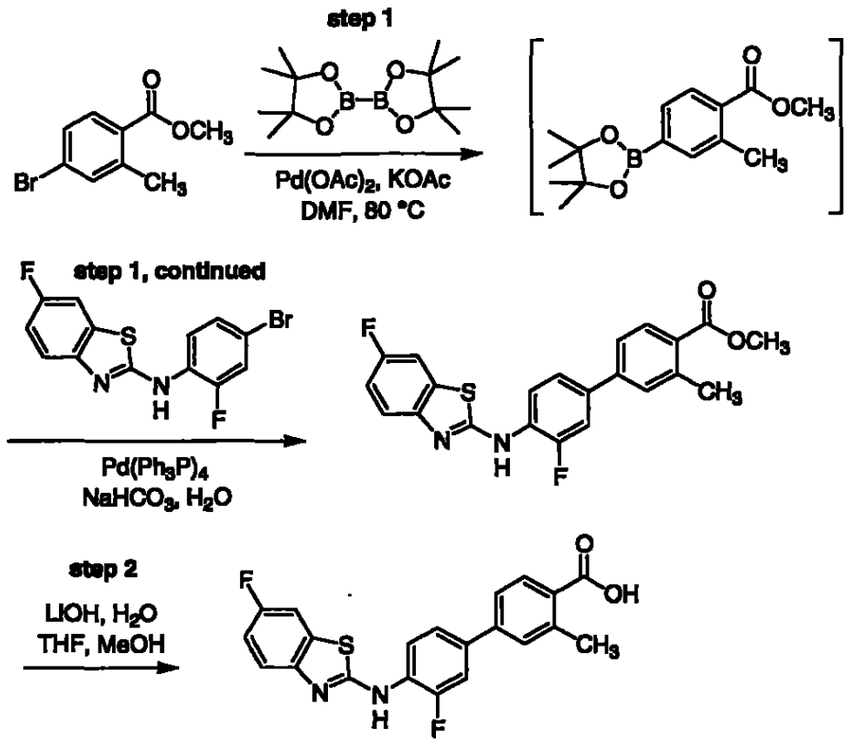
[105] As shown in Reaction Scheme 5, methyl 3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylate (0.64 g, 1.6 mmol) was suspended in THF (10 mL), MeOH (10 mL) and water (5 mL), and LiOH (0.39 g, 16.2 mmol) was added. The reaction mixture was heated at 50°C until dissolution was achieved, and then the mixture was stirred for 3 days at rt. The reaction mixture was brought to pH 4 with 1N HCl and was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with water (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. This yielded 0.518 g (84%) of the desired product as an off-white solid. LC/MS *m/z* 383.3 (MH^+), retention time 3.83 min. ^1H NMR (400 MHz, DMSO-d_6) δ 7.18 (t, 1H), 7.59-8.00 (m, 8H), 8.70 (t, 1H), 10.50 (bs, 1H), 12.95 (bs, 1H).

[106] Intermediate VI-2: 3'-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methyl biphenyl-4-carboxylic acid

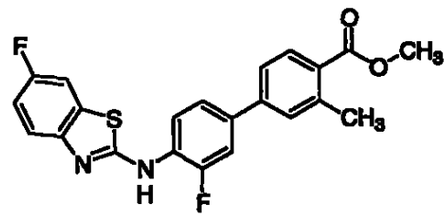


The preparation of 3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-carboxylic acid is described below in Reaction Scheme 6.

[107] **Reaction Scheme 6**



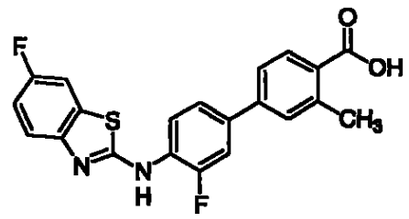
[108] Step 1. Preparation of methyl 3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-carboxylate



[109] As shown in Reaction Scheme 6, a mixture of bis(pinacolato)diboron (0.55 g, 2.2 mmol), methyl 4-bromo-2-methylbenzoate (0.50 g, 2.2 mmol), palladium(II) acetate (0.01 g, 0.07 mmol), and KOAc (0.64 g, 6.6 mmol) in DMF (7.5 mL) was degassed with argon for 30 min at rt. The mixture was then heated at 80°C for 4 h. After cooling the mixture to rt, *N*-(4-bromo-2-fluorophenyl)-6-fluoro-1,3-benzothiazol-2-amine (0.74 g, 2.2 mmol), tetrakis(triphenylphosphine)palladium(0) (0.08 g, 0.07 mmol), and saturated aqueous $NaHCO_3$ (5 mL) were added. The mixture was heated at 85°C overnight. The mixture was poured into ice water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (20% EtOAc in hexanes). This yielded 0.345 g (39%) of the title compound.

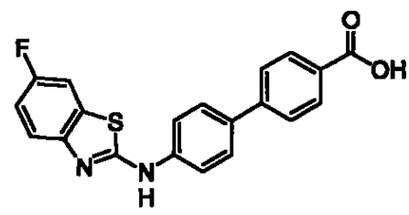
LC/MS *m/z* 411.3 (MH^+); retention time 4.15 min. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 2.62 (s, 3H), 3.90 (s, 3H), 7.10 (t, 1H), 7.39-7.53 (m, 5H), 7.62-7.70 (m, 1H), 7.99 (d, 1H), 8.58 (t, 1H).

[110] Step 2. Preparation of 3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-carboxylic acid

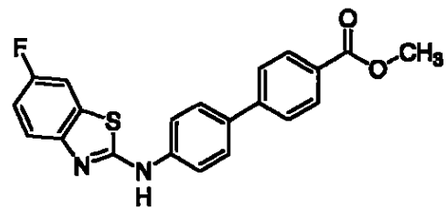


[111] As shown in Reaction Scheme 6, methyl 3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-carboxylate (0.38 g, 0.67 mmol) was suspended in THF (5 mL), MeOH (5 mL), and water (2.5 mL), and NaOH (0.27 g, 6.7 mmol) was added. The reaction mixture was heated at 50°C for 3 h. Upon cooling to rt, the reaction mixture was concentrated in vacuo, acidified with 2N HCl, and the resulting solid was collected by filtration. This yielded 0.33 g (quantitative) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.62 (s, 3H), 7.10 (t, 1H), 7.49-7.58 (m, 5H), 7.65-7.75 (m, 1H), 8.10 (d, 1H), 8.58 (t, 1H), 10.85 (br, 1H).

[112] Intermediate VI-3: 4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylic acid



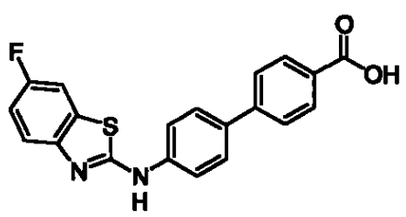
[113] Step 1. Preparation of methyl 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylate



[114] A mixture of bis(pinacolato)diboron (0.35 g, 1.4 mmol), methyl 4-bromobenzoate (0.30 g, 1.4 mmol), palladium(II) acetate (0.01 g, 0.04 mmol), and KOAc (0.41 g, 4.2 mmol) in DMF (7.5 mL) was degassed with argon for 30 min at rt. The mixture was then heated at 80°C for 4 h.

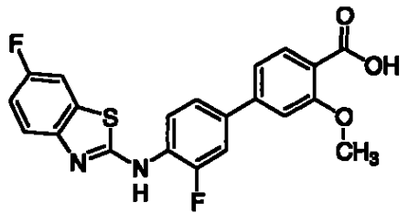
After the mixture was cooled to rt, *N*-(4-bromophenyl)-6-fluoro-1,3-benzothiazol-2-amine (0.45 g, 1.4 mmol), tetrakis(triphenylphosphine)palladium(0) (0.05 g, 0.04 mmol), and saturated aqueous $NaHCO_3$ (5 mL) were added. The mixture was heated at 85°C overnight. Upon cooling to rt, the mixture was diluted with EtOAc. The combined organic phases were separated, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (25% EtOAc in hexanes) yielded 0.094 g (18%) of the title compound. *LC/MS m/z* 379.3 (MH^+); retention time 3.87 min. ^1H NMR (400 MHz, CD_3OD) δ 3.93 (s, 3H), 7.05 (t, 1H), 7.39-7.81 (m, 8H), 8.03 (d, 2H).

[115] Step 2. Preparation of 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylic acid

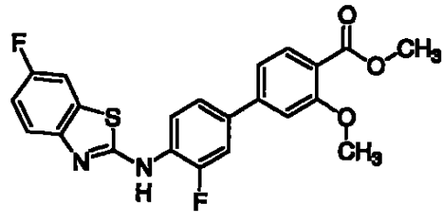


[116] Methyl 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylate (94 mg, 0.25 mmol) was suspended in THF (3 mL), MeOH (3 mL), and water (1.5 mL), and NaOH (0.10 g, 2.5 mmol) was added. The reaction mixture was heated at 50°C for 3 h. Upon cooling to rt, the reaction mixture was concentrated in vacuo, acidified with 2N HCl, and the resulting solid was collected by filtration. This yielded 90 mg (99%) of the title compound. *LC/MS m/z* 365.2 (MH^+), retention time 3.46 min. ^1H NMR (400 MHz, DMSO-d_6) δ 7.08 (t, 1H), 7.49-7.80 (m, 6H), 7.82-8.01 (m, 4H), 10.75 (br, 1H).

[117] Intermediate VI-4: 3'-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxy biphenyl-4-carboxylic acid

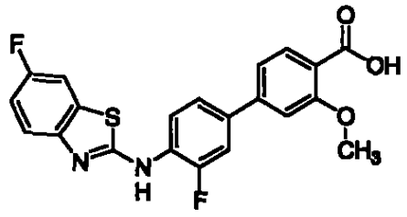


[118] Step 1. Preparation of methyl 3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxy biphenyl-4-carboxylate



[119] A mixture of bis(pinacolato)diboron (1.40 g, 5.51 mmol), methyl 4-bromo-2-methoxybenzoate (1.35 g, 5.51 mmol), palladium(II) acetate (0.04 g, 0.17 mmol), and KOAc (1.62 g, 16.5 mmol) in DMF (10 mL) was degassed with argon for 30 min at rt. The mixture was then heated at 80°C for 4 h. After the mixture was cooled to rt, *N*-(4-bromo-2-fluorophenyl)-6-fluoro-1,3-benzothiazol-2-amine (1.88 g, 5.51 mmol), tetrakis(triphenylphosphine)palladium(0) (0.19 g, 0.17 mmol), and saturated aqueous $NaHCO_3$ (5 mL) were added. The mixture was heated at 85°C overnight. The mixture was poured into ice water and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, concentrated in vacuo, and purified by column chromatography (25% EtOAc in hexanes). This yielded 0.431 g (18%) of the title compound. LC/MS *m/z* 427.3 (MH^+), retention time 3.82 min. ^1H NMR (400 MHz, CD_2Cl_2) δ 3.81 (s, 3H), 4.03 (s, 3H), 7.19-7.23 (m, 3H), 7.41-7.64 (m, 4H), 7.82 (d, 1H), 8.31 (t, 1H).

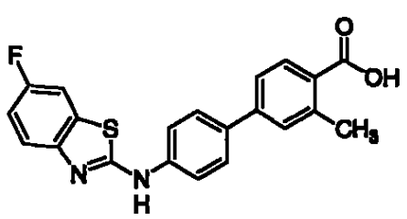
[120] Step 2. Preparation of 3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxy biphenyl-4-carboxylic acid



[121] Methyl 3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-carboxylate (0.43 g, 1.01 mmol) was suspended in THF (10 mL), MeOH (5 mL) and water (5 mL), and NaOH (0.40 g, 10 mmol) was added. The reaction mixture was stirred at rt for 18 h. The reaction mixture was concentrated under reduced pressure, acidified with 2N HCl, and the resulting solid was collected by filtration. This yielded 0.41 g (99%) of the title compound as a light brown solid. LC/MS *m/z* 413.3 (MH^+), retention time 3.44 min. ^1H NMR (400 MHz, DMSO-d_6) δ 3.91 (s, 3H), 7.17 (t, 1H), 7.24-7.29 (m, 2H), 7.58-7.78 (m, 5H), 8.63 (t, 1H), 10.45 (br, 1H).

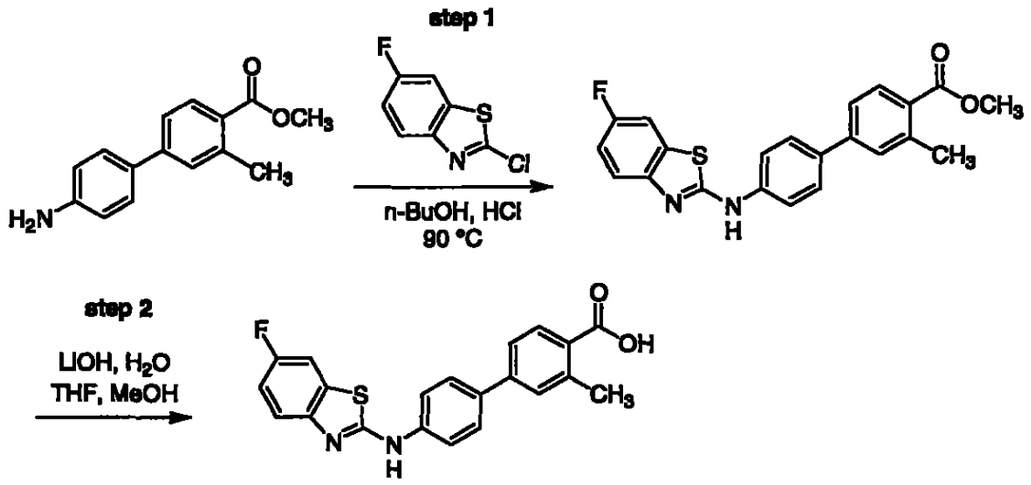
Preparation of Intermediate Compounds of Formula (VI) by Method B

[122] Intermediate VI-5: 4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-carboxylic acid

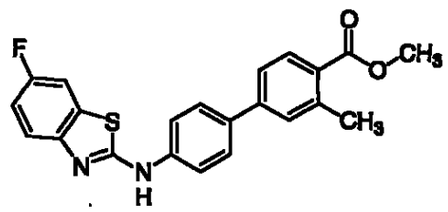


The preparation of 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-carboxylic acid is described below in Reaction Scheme 7.

[123] **Reaction Scheme 7**

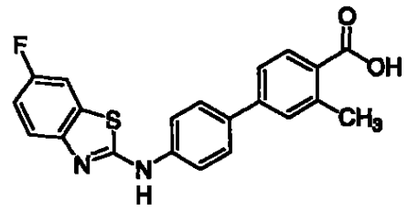


[124] Step 1. Preparation of methyl 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-carboxylate



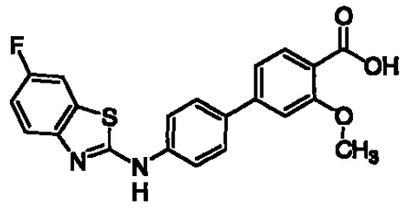
[125] As shown in Reaction Scheme 7, a mixture of methyl 4'-amino-3-methylbiphenyl-4-carboxylate (0.34 g, 1.40 mmol) and 2-chloro-6-fluoro-1,3-benzothiazole (0.26 g, 1.40 mmol) in n-butanol (4 mL) was heated to 60-70°C, and then 4N HCl in 1,4-dioxane (0.16 mL, 0.63 mmol) was added dropwise with stirring. The reaction mixture was heated at 90°C for 18 h. Upon cooling to rt, the reaction mixture was concentrated in vacuo. The residue was triturated with ethanol and collected by filtration, yielding 0.32 g (58%) of the title compound as a pale yellow solid. LC/MS *m/z* 393.3 (MH^+), retention time 4.02 min. ^1H NMR (400 MHz, CD_2Cl_2) δ 2.62 (s, 3H), 3.95 (s, 3H), 7.05 (t, 1H), 7.39-7.60 (m, 4H), 7.65 (s, 4H), 7.96 (d, 1H).

[126] Step 2. Preparation of 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-carboxylic acid

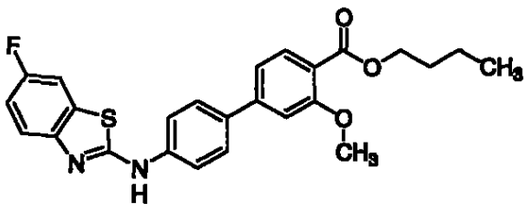


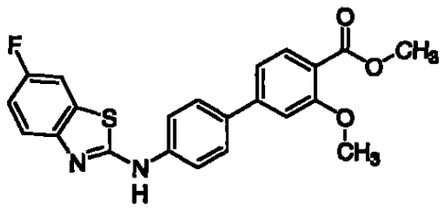
[127] As shown in Reaction Scheme 7, methyl 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-carboxylate (0.25 g, 0.65 mmol) was suspended in THF (5 mL), MeOH (5 mL) and water (2.5 mL), and NaOH (0.26 g, 6.5 mmol) was added. The reaction mixture was heated at 50°C for 3 h. Upon cooling to rt, the reaction mixture was concentrated in vacuo, acidified with 2N HCl, and the resulting solid was collected by filtration. This yielded 0.25 g (quantitative) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.62 (s, 3H), 7.05 (t, 1H), 7.57-7.90 (m, 9H), 10.62 (br, 1H)

[128] Intermediate VI-6: 4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-carboxylic acid



[129] Step 1. Preparation of butyl 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-carboxylate and methyl 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-carboxylate

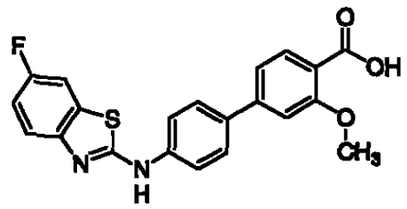




[130] A mixture of methyl 4'-amino-3-methoxybiphenyl-4-carboxylate (0.27 g, 1.06 mmol) and 2-chloro-6-fluoro-1,3-benzothiazole (0.20 g, 1.06 mmol) in n-butanol (8 mL) was heated to 60-70°C, and then 4N HCl in 1,4-dioxane (0.12 mL, 0.48 mmol) was added dropwise with stirring. The reaction mixture was heated at 90°C for 18 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (25% EtOAc in hexanes), yielding 0.209 g (44%) of butyl 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-

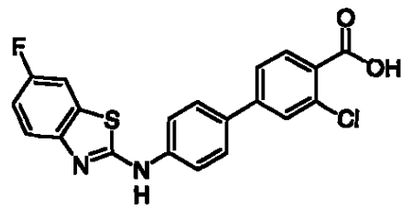
methoxybiphenyl-4-carboxylate, and 0.132 g (30%) of methyl 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-carboxylate [LC/MS *m/z* 409.3 (MH^+), retention time = 3.67 min, *m/z* 451.3 (MH+), retention time = 4.25 min. ^1H NMR (400 MHz, CD_2Cl_2) δ 3.85 (s, 3H), 4.00 (s, 3H), 7.05-7.26 (m, 3H), 7.42 (d, 1H), 7.61-7.64 (m, 1H), 7.76 (s, 4H), 7.90 (d, 1H)].

[131] Step 2. Preparation of 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-carboxylic acid

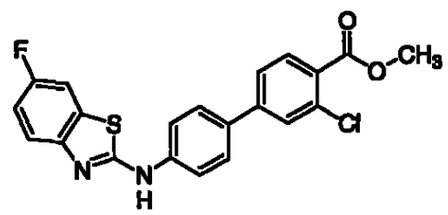


[132] Butyl 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-carboxylate (0.30 g, 0.43 mmol) and methyl 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-carboxylate (0.13 g, 0.25 mmol) were combined in THF (6 mL), MeOH (6 mL) and water (3 mL), and then NaOH (0.09 g, 2.1 mmol) was added. The reaction mixture was heated at 50°C for 3 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure, acidified, and the resulting solid was collected by filtration. This yielded 0.286 g (87%) of the title compound. LC/MS *m/z* 395.2 (MH^+), retention time 3.30 min. ^1H NMR (400 MHz, DMSO-d_6) δ 3.90 (s, 3H), 7.12-7.33 (m, 3H), 7.61-7.90 (m, 7H), 10.62 (br, 1H).

[133] Intermediate VI-7: 4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]-3-chlorobiphenyl-4-carboxylic acid

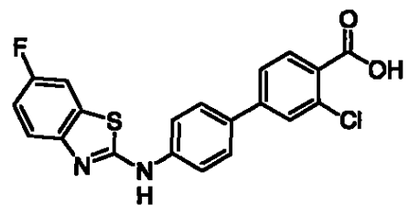


[134] Step 1. Preparation of methyl 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-chlorobiphenyl-4-carboxylate



[135] A mixture of methyl 4'-amino-3-chlorobiphenyl-4-carboxylate (0.45 g, 1.7 mmol) and 2-chloro-6-fluoro-1,3-benzothiazole (0.32 g, 1.7 mmol) in n-butanol (8 mL) was heated to 60-70°C, and then 4N HCl in 1,4-dioxane (0.19 mL, 0.77 mmol) was added dropwise with stirring. The reaction mixture was heated at 90°C for 18 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure. The residue was triturated with ethanol, and the solid was collected by filtration. This yielded 0.399 g (56%) of the title compound as a beige solid. *LC/MS m/z* 411 (MH^+), retention time 4.03 min. ^1H NMR (400 MHz, DMSO-d_6) δ 3.85 (s, 3H), 7.12 (t, 1H), 7.67-7.87 (m, 9H), 10.62 (br, 1H).

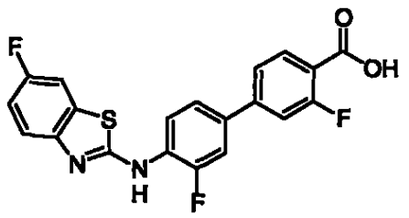
[136] Step 2. Preparation of 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-chlorobiphenyl-4-carboxylic acid



[137] Methyl 4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-chlorobiphenyl-4-carboxylate (0.30 g, 0.71 mmol) was suspended in THF (5 mL), MeOH (5 mL) and water (2.5 mL), and then NaOH (0.28 g, 7.1 mmol) was added. The reaction mixture was heated at 50°C for 3 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure, acidified, and the resulting solid was collected by filtration. This yielded 0.34 g (quantitative) of the title compound. *LC/MS m/z* 399.2 (MH^+), retention time 3.53 min.

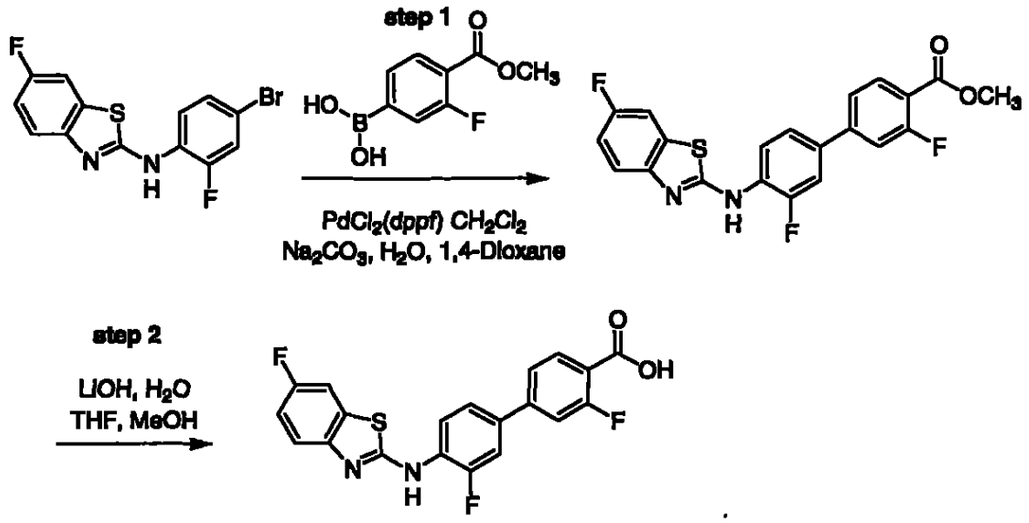
Preparation of Intermediate Compounds of Formula (VI) by Method A

[138] Intermediate VI-8: 3,3'-Difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylic acid



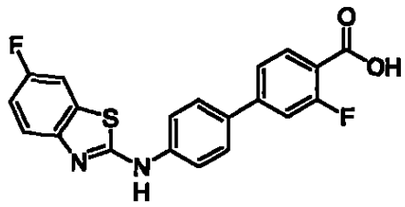
The preparation of 3,3'-difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylic acid is described below in Reaction Scheme 8.

[139] **Reaction Scheme 8**



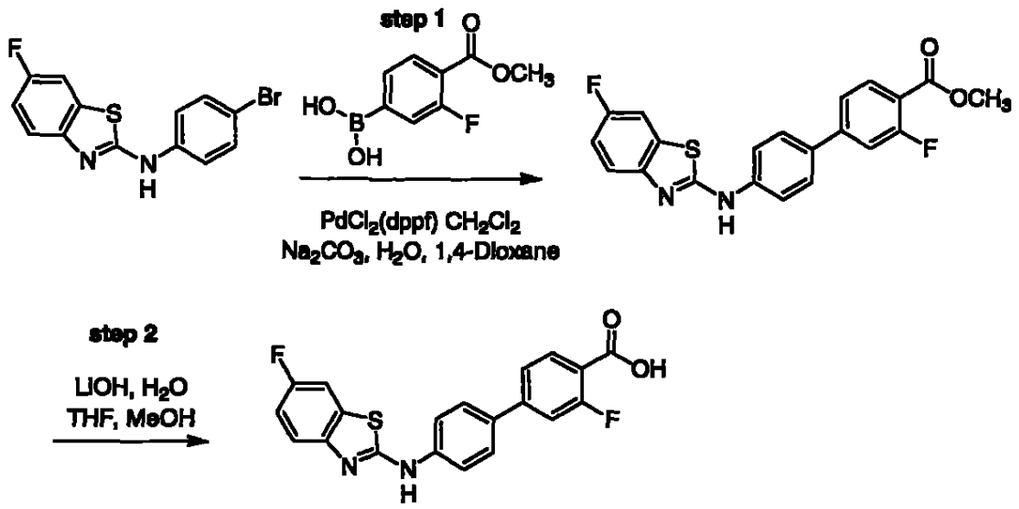
[140] As shown in Reaction Scheme 8, Intermediate VI-8 (3,3'-difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylic acid) was prepared using a method similar to that employed in the preparation of Intermediate VI-1 using *N*-(4-bromo-2-fluorophenyl)-6-fluoro-1,3-benzothiazol-2-amine and commercially available [3-fluoro-4-(methoxycarbonyl)phenyl]boronic acid as starting materials.

[141] **Intermediate VI-9: 3-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylic acid**



The preparation of 3-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylic acid is described below in Reaction Scheme 9.

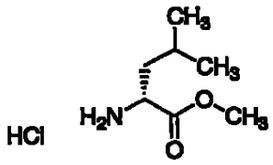
[142] **Reaction Scheme 9**



As shown in Reaction Scheme 9, Intermediate VI-9 (3-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylic acid) was prepared using a method similar to that employed in the preparation of Intermediate VI-1 using N-(4-bromophenyl)-6-fluoro-1,3-benzothiazol-2-amine and commercially available [3-fluoro-4-(methoxycarbonyl)phenyl]boronic acid as starting materials.

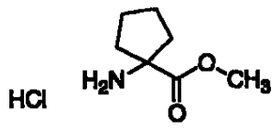
Preparation of Compounds of Formula (VII)

[143] **Intermediate VIII-1: Methyl D-leucinate hydrochloride**



[144] D-Leucine (3.00 g, 22.9 mmol) was added to a solution of acetyl chloride (1.70 mL, 23.9 mmol) in methanol (30 mL). The reaction mixture was allowed to stir for 18 h and then concentrated under reduced pressure. This yielded 3.8 g (91%) of the title compound. ^{1}H NMR (400 MHz, CD_3OD) δ 0.99 (dd, 6H), 1.63-1.87 (m, 3H), 4.10 (dd, 1H), 3.81 (s, 3H).

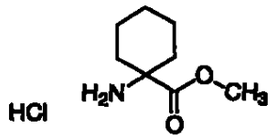
[145] **Intermediate VIII-2: Methyl 1-aminocyclopentanecarboxylate hydrochloride**



[146] 1-Aminocyclopentanecarboxylic acid (1.00 g, 7.74 mmol) was added to a solution of acetyl chloride (0.60 mL, 8.44 mmol) in methanol (10 mL). The reaction mixture was allowed to stir for

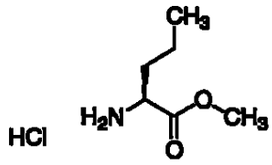
18 h and then concentrated under reduced pressure. This yielded 1.35 g (97%) of the title compound. ^{1}H NMR (400 MHz, CD_3OD) δ 1.80-2.00 (m, 6H), 2.34-2.39 (m, 2H), 3.82 (s, 3H).

[147] **Intermediate VIII-3: Methyl 1-aminocyclohexanecarboxylate hydrochloride**



[148] 1-Aminocyclohexanecarboxylic acid (1.00 g, 6.98 mmol) was added to a solution of acetyl chloride (0.60 mL, 8.44 mmol) in methanol (10 mL). The reaction mixture was allowed to stir for 18 h and then concentrated under reduced pressure. ^{1}H NMR (400 MHz, CD_3OD) δ 1.42-1.82 (m, 8H), 2.08-2.20 (m, 2H), 3.82 (s, 3H).

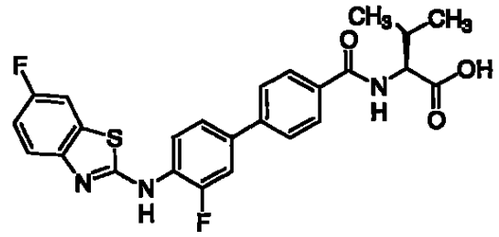
[149] **Intermediate VIII-4: Methyl L-norvalinate hydrochloride**



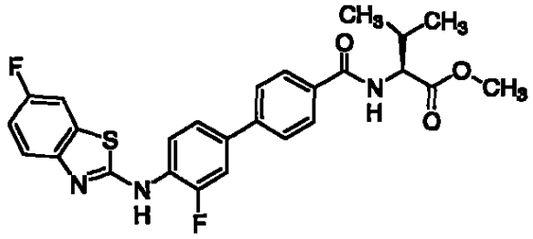
[150] L-Norvaline (0.82 g, 6.98 mmol) was added to a solution of acetyl chloride (0.60 mL, 8.44 mmol) in methanol (10 mL). The reaction mixture was allowed to stir for 18 h and then concentrated under reduced pressure. ^{1}H NMR (400 MHz, CD_3OD) δ 1.0 (t, 3H), 1.35-1.50 (m, 2H), 1.80-2.00 (m, 2H), 3.82 (s, 3H).

Preparation of Compounds of Formula (I)

[151] Example 1: *N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine

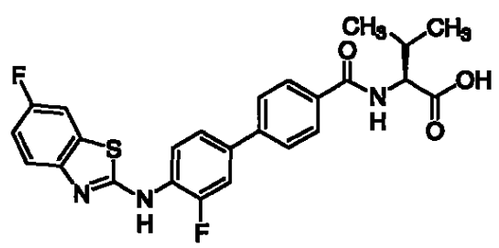


[152] Step 1. Preparation of methyl *N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino] biphenyl-4-yl}carbonyl)-L-valinate



[153] 3'-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-carboxylic acid (0.084 g, 0.22 mmol) and L-valine methyl ester hydrochloride (0.044 g, 0.26 mmol) were suspended in CH_2Cl_2 (5 mL), and triethylamine (0.04 mL, 0.26 mmol), 1-hydroxybenzotriazole (0.0296 g, 0.22 mmol), and *N,N'*-diisopropylcarbodiimide (0.030 mL, 0.22 mmol) were added. DMF (2.0 mL) was added to achieve dissolution, and the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with EtOAc (50 mL) and was washed with water (2 x 50 mL) and brine (50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (Biotage® system; 30-40% EtOAc/Hexanes gradient). This yielded 90.4 mg (83%) of the desired product as a white solid.

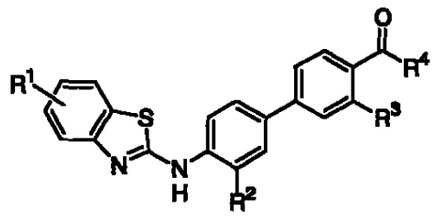
[154] Step 2. Preparation of *N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine



[155] Methyl *N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valinate (84.2 mg, 0.17 mmol) was suspended in THF (2.5 mL), MeOH (2.5 mL) and water (1 mL), and LiOH (40.7 mg, 1.70 mmol) was added. The reaction mixture was heated at 50°C for 2 h. Upon cooling to rt, the reaction mixture was brought to pH 3 with 1N HCl and was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with water (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. This yielded 72.3 mg (88%) of the title compound as a white solid. LC/MS *m/z* 482.3 (MH^+), retention time 3.46 min. ^1H NMR (400 MHz, DMSO-d_6) δ 0.99 (dd, 6H), 2.19-2.24 (m, 1H), 4.30 (dd, 1H), 7.18 (t, 1H), 7.60-7.84 (m, 6H), 7.88 (d, 2H), 8.42 (d, 1H), 8.66 (t, 1H), 10.42 (s, 1H).

[156] By using the methods described above and by substituting the appropriate starting materials, compounds of Formula (I), listed in Table 1a below, were similarly prepared.

[157] **Table 1a. Preparative Examples of Compounds of Formula (I)**



Example No.	R^1	R^2	R^3	R^4	LC-MS Ret. Time (min)	LC-MS $[M+H]^+$	Method
1	6-F	F	H	L-Val-OH	3.46	482.3	A
2	6-F	H	H	L-Ala-OH	3.50	436.3	A
3	6-F	F	H	L-Ala-OH	3.55	454.3	A
4	6-F	H	H	L-Val-OH	3.72	464.3	A
5	6-F	H	Cl	L-Val-OH	3.46	498.2	B
6	6-F	F	CH_3	L-Val-OH	3.47	496.2	A
7	6-F	F	OMe	L-Val-OH	3.60	512.4	A
8	6-F	H	H	L-Leu-OH	3.86	478.3	A
9	6-F	F	H	L-Leu-OH	3.93	496.3	A
10	6-F	H	OMe	L-Leu-OH	3.64	508.2	B
11	6-F	F	OMe	L-Leu-OH	3.75	526.4	A
12	6-F	H	Cl	L-Leu-OH	3.62	512.2	B

Example No.	R^1	R^2	R^3	R^4	LC-MS Ret. Time (min)	LC-MS $[M+H]^+$	Method
13	6-F	H	CH_3	L-Leu-OH	3.55	492.2	B
14	6-F	F	CH_3	L-Leu-OH	3.60	510.4	A
15	6-F	H	H	D-Leu-OH	3.48	478.2	A
16	6-F	F	H	D-Leu-OH	3.58	496.2	A
17	6-F	H	H	L-Ile-OH	3.52	478.2	A
18	6-F	F	H	L-Ile-OH	3.64	496.4	A
19	6-F	F	OMe	L-Ile-OH	3.75	526.4	A
20	6-F	H	H	L-Phe-OH	3.85	512.3	A
21	6-F	F	H	L-Phe-OH	3.93	530.2	A
22	6-F	H	OMe	L-Phe-OH	3.63	508.2	B
23	6-F	H	CH_3	L-Phe-OH	3.51	526.2	A
24	6-F	F	CH_3	L-Phe-OH	3.61	544.3	A
25	6-F	H	Cl	L-Phe-OH	3.60	546.1	B
26	6-F	H	H	L-Pro-OH	3.52	462.2	A
27	6-F	F	H	L-Pro-OH	3.58	480.2	A
28	6-F	H	OMe	L-Pro-OH	3.20	492.1	B
29	6-F	H	Cl	L-Pro-OH	3.32	496.1	B
30	6-F	H	CH_3	L-Pro-OH	3.52	476.1	B
31	6-F	F	CH_3	L-Pro-OH	3.31	494.3	A

[158] **Table 1b. IUPAC Names for Compounds in Table 1a**

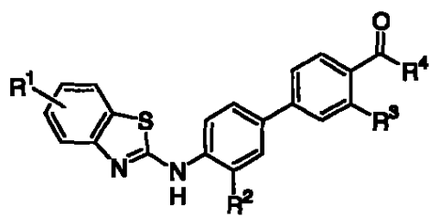
Example No.	IUPAC Name
1	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine
2	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine
3	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine
4	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine

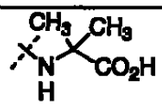
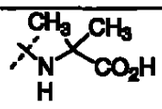
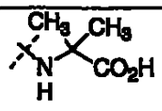
Example No.	IUPAC Name
5	*N*-({3-chloro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine
6	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine
7	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine
8	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine
9	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine
10	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-leucine
11	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-leucine
12	*N*-({3-chloro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine
13	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-leucine
14	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-leucine
15	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-D-leucine
16	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-D-leucine
17	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-isoleucine
18	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-isoleucine
19	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-isoleucine
20	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-phenylalanine
21	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-phenylalanine
22	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-phenylalanine
23	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-phenylalanine
24	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-phenylalanine

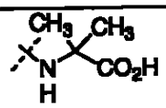
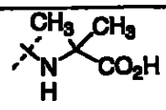
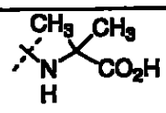
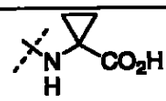
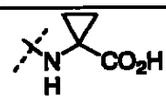
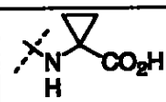
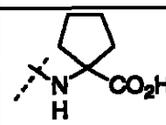
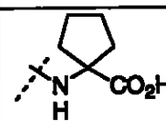
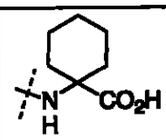
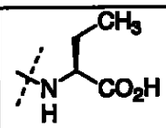
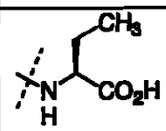
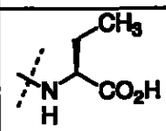
Example No.	IUPAC Name
25	*N*-({3-chloro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-phenylalanine
26	1-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-proline
27	1-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-proline
28	1-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-proline
29	1-({3-chloro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-proline
30	1-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-proline
31	1-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-proline

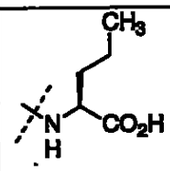
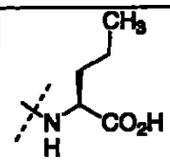
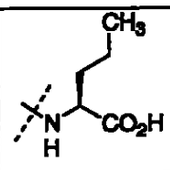
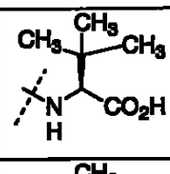
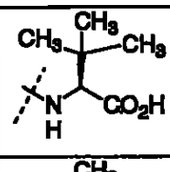
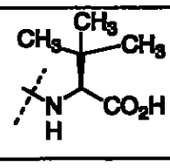
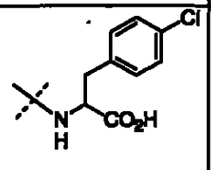
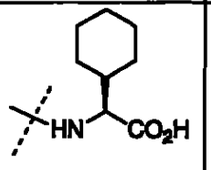
[159] By using the methods described above and by substituting the appropriate starting materials, compounds of Formula (I), listed in Table 2a below, were similarly prepared.

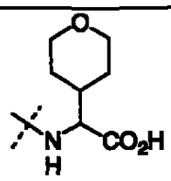
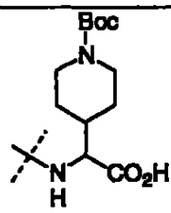
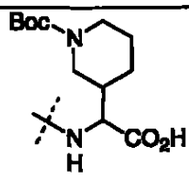
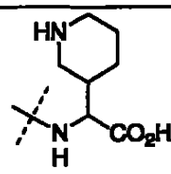
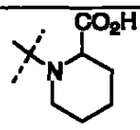
[160] **Table 2a. Preparative Examples of Compounds of Formula (I)**



Example No.	R^1	R^2	R^3	R^4	LC-MS Ret. Time (min)	LC-MS $[M+H]^+$	Method
32	6-F	H	H		3.57	450.2	A
33	6-F	F	H		3.64	468.2	A
34	6-F	H	OCH_3		3.35	480.1	B

Example No.	R^1	R^2	R^3	R^4	LC-MS Ret. Time (min)	LC-MS $[M+H]^+$	Method
35	6-F	H	Cl		3.30	484.1	B
36	6-F	H	CH_3		3.24	464.2	B
37	6-F	F	CH_3		3.28	482.3	A
38	6-F	H	H		3.48	448.2	A
39	6-F	F	H		3.23	466.3	A
40	6-F	F	OCH_3		3.34	496.3	A
41	6-F	H	H		3.74	476.3	A
42	6-F	F	H		3.49	494.3	A
43	6-F	H	H		3.87	490.3	A
44	6-F	H	H		3.25	450.1	A
45	6-F	F	H		3.37	468.3	A
46	6-F	F	OCH_3		3.50	498.4	A

Example No.	R^1	R^2	R^3	R^4	LC-MS Ret. Time (min)	LC-MS $[M+H]^+$	Method
47	6-F	H	H		3.76	464.3	A
48	6-F	F	H		3.55	482.4	A
49	6-F	F	OCH_3		3.63	512.3	A
50	6-F	H	H		3.52	478.2	A
51	6-F	F	H		3.63	496.3	A
52	6-F	F	OCH_3		3.73	526.4	A
53	6-F	H	H		3.68	546.1	A
54	6-F	H	H		3.68	504.2	A

Example No.	R^1	R^2	R^3	R^4	LC-MS Ret. Time (min)	LC-MS $[M+H]^+$	Method
55	6-F	H	H		3.15	506.2	A
56	6-F	H	H		3.60	605.0	A
57	6-F	H	H		3.65	605.1	A
58	6-F	H	H		2.98	505.2	A
59	6-F	F	H		3.80	494.2	A

[161] **Table 2b. IUPAC Names for Compounds in Table 2a**

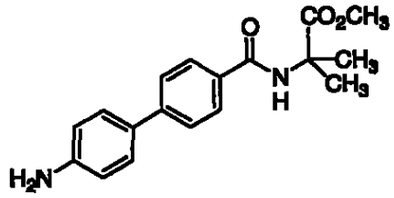
Example No.	IUPAC Name
32	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine
33	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine
34	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-2-methylalanine
35	*N*-({3-chloro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine
36	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-2-methylalanine

Example No.	IUPAC Name
37	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-2-methylalanine
38	1-[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]cyclopropanecarboxylic acid
39	1-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]cyclopropanecarboxylic acid
40	1-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)amino]cyclopropanecarboxylic acid
41	1-[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]cyclopentanecarboxylic acid
42	1-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]cyclopentanecarboxylic acid
43	1-[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]cyclohexanecarboxylic acid
44	(2S)-2-[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid
45	(2S)-2-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid
46	(2S)-2-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)amino]butanoic acid
47	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-norvaline
48	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-norvaline
49	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-norvaline
50	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-methyl-L-valine
51	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-methyl-L-valine
52	*N*-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-3-methyl-L-valine
53	4-chloro-*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)phenylalanine
54	(2S)-cyclohexyl[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]acetic acid
55	[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino](tetrahydro-2*H*-pyran-4-yl)acetic acid
56	[1-(tert-butoxycarbonyl)piperidin-4-yl][({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]acetic acid

Example No.	IUPAC Name
57	[1-(tert-butoxycarbonyl)piperidin-3-yl][({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]acetic acid
58	[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino](piperidin-3-yl)acetic acid
59	1-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)piperidine-2-carboxylic acid

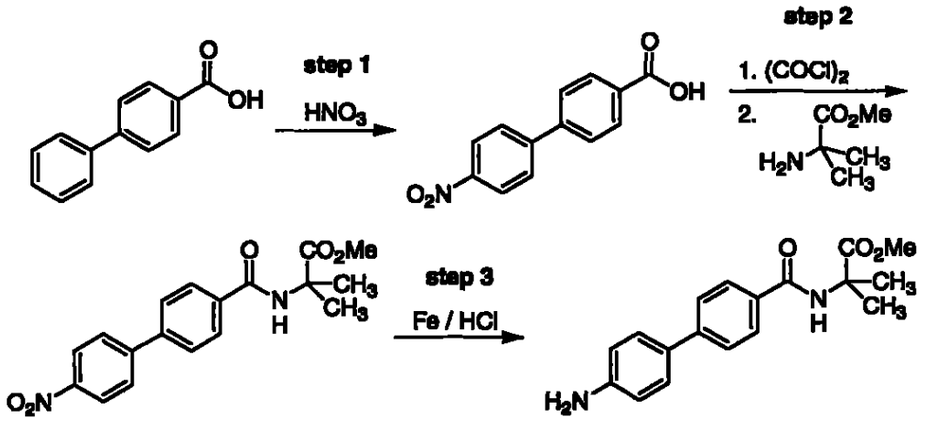
Preparation of Intermediate Compounds of Formula (XIII) by Method C

[162] **Intermediate XIII-1: Methyl *N*-[(4'-aminobiphenyl-4-yl)carbonyl]-2-methylalaninate**

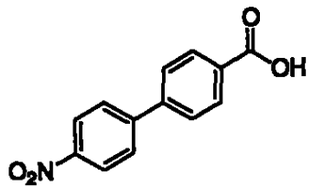


The preparation of methyl *N*-[(4'-aminobiphenyl-4-yl)carbonyl]-2-methylalaninate is described below in Reaction Scheme 10.

[163] **Reaction Scheme 10**

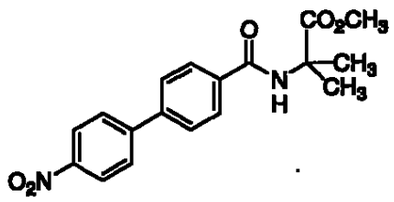


[164] Step 1. Preparation of 4'-nitro-1,1'-biphenyl-4-carboxylic acid



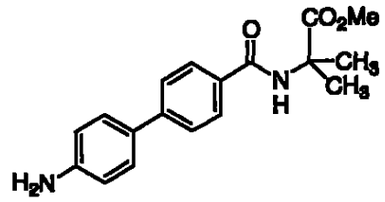
[165] As shown in Reaction Scheme 10, to ice-cold nitric acid was added 4-biphenylcarboxylic acid (9.4 g, 20.0 mmol), and the resulting mixture was stirred with cooling in an ice-water bath for 1 h. The mixture was poured into ice-water and filtered. The collected solid was suspended in ethanol and heated at reflux for 2 h. The mixture was filtered hot, washed with ethanol and dried under high vacuum to give 4'-nitro-1,1'-biphenyl-4-carboxylic acid (2.3 g, 47%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, 2 H), 8.01 (d, 2 H), 8.05 (d, 2 H), 8.31 (d, 2 H), 13.12 (d, 2 H).

[166] Step 2. Preparation of methyl 2-methyl-*N*-[(4'-nitrobiphenyl-4-yl)carbonyl]alaninate



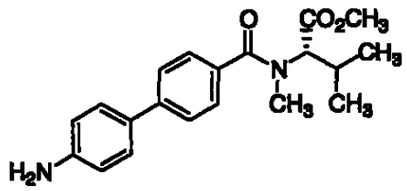
[167] As shown in Reaction Scheme 10, 4'-nitro-1,1'-biphenyl-4-carboxylic acid (4.66 g, 19.2 mmol) was dissolved in methylene chloride (110 mL), and then oxalyl chloride (2.51 mL, 28.7 mmol) was added, followed by 3 drops of *N,N*-dimethylformamide. The resulting mixture was stirred at rt for 45 min, concentrated under reduced pressure, and further dried under vacuum for 30 min. The residue was dissolved in methylene chloride (75 mL) and added dropwise to an ice-cold mixture of methyl 2-methylalaninate hydrochloride (3.83 g, 24.9 mmol), methylene chloride (75 mL), and triethylamine (6.68 mL, 47.9 mmol). The resulting solution was stirred at rt for 1 h and then at 55°C for 2 h. The mixture was allowed to cool to rt and was then washed with 1*N* aqueous HCl solution (5 mL) and water (2 x 20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage® system, 4:1 hexanes/EtOAc) to afford methyl 2-methyl-*N*-[(4'-nitrobiphenyl-4-yl)carbonyl]alaninate (6.21 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (s, 6 H), 3.82 (s, 3 H), 6.89 (broad s, 1 H), 7.69 (d, 2 H), 7.77 (d, 2 H), 7.92 (d, 2 H), 8.31 (d, 2 H); LC-MS *m/z* 342.9 (MH^+), retention time 2.98 minutes.

[168] Step 3. Preparation of methyl *N*-[(4'-aminobiphenyl-4-yl)carbonyl]-2-methylalaninate

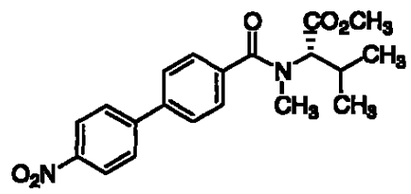


[169] As shown in Reaction Scheme 10, to a solution of methyl 2-methyl-*N*-[(4'-nitrobiphenyl-4-yl)carbonyl]alaninate (1.59 g, 4.6 mmol) in 85% ethanol (50 mL) was added iron powder (2.59 g, 46.4 mmol) and 2 M aqueous HCl solution (2.32 mL, 4.6 mmol). The resulting mixture was heated at reflux for 2 h. The mixture was then filtered through a pad of Celite® and concentrated under reduced pressure to afford *N*-[(4'-aminobiphenyl-4-yl)carbonyl]-2-methylalaninate as a yellow solid (2.48 g, 99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.44 (s, 6 H), 3.57 (s, 3 H), 5.33 (broad s, 2 H), 6.61 (d, 2 H), 7.41 (d, 2 H), 7.58 (d, 2 H), 7.83 (d, 2 H), 8.54 (broad s, 1 H); LC-MS *m/z* 313.2 (MH^+), retention time 1.54 minutes.

[170] Intermediate XIII-2: Methyl *N*-[(4'-aminobiphenyl-4-yl)carbonyl]-*N*-methyl-L-valinate



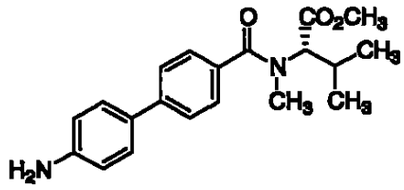
[171] Step 1. Preparation of methyl *N*-methyl-*N*-[(4'-nitro-1,1'-biphenyl-4-yl)carbonyl]-L-valinate



[172] 4'-Nitro-1,1'-biphenyl-4-carboxylic acid (0.50 g, 2.0 mmol) was dissolved in methylene chloride (25 mL), and then oxalyl chloride (0.27 mL, 3.1 mmol) was added, followed by one drop of *N,N*-dimethylformamide. The resulting mixture was heated at 50°C for 1 h, concentrated under reduced pressure, and further dried under vacuum for 30 min. The residue was dissolved in methylene chloride (20 mL) and added dropwise to an ice-cold mixture of methyl *N*-methyl-L-valinate hydrochloride (0.48 g, 2.6 mmol), methylene chloride (50 mL), and triethylamine (1.44 mL, 10.2 mmol). The resulting solution was stirred on ice for 1 h and then at rt overnight. The mixture was diluted with methylene chloride and washed with 1*N* aqueous HCl solution and brine. The organic layer was separated and concentrated under reduced pressure. The residue was purified by

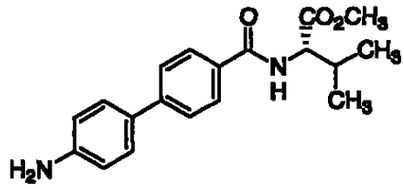
flash chromatography (Biotage® system, 3:1 hexanes/EtOAc) to afford methyl *N*-methyl-*N*-[(4'-nitro-1,1'-biphenyl-4-yl)carbonyl]-L-valinate (0.70 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (dd, 3 H), 1.06 (dd, 3 H), 2.31 (m, 1 H), 3.02 (d, 3 H), 3.77 (d, 3 H), 3.94 (d, 0.5 H), 4.98 (d, 0.5 H), 7.52 (m, 2 H), 7.64 (m, 2 H), 7.72 (t, 2 H), 8.27 (d, 2 H); LC-MS *m/z* 371.2 (MH^+), retention time 3.27 minutes.

[173] Step 2. Preparation of methyl *N*-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]-*N*-methyl-L-valinate

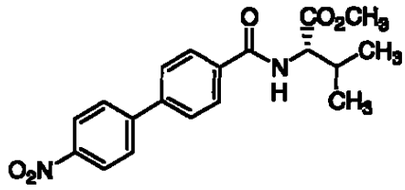


[174] To a solution of methyl *N*-methyl-*N*-[(4'-nitro-1,1'-biphenyl-4-yl)carbonyl]-L-valinate (0.70 g, 1.9 mmol) in 85% ethanol (20 mL) was added iron powder (1.05 g, 18.9 mmol) and 2N aqueous HCl solution (0.41 mL). The resulting mixture was heated at reflux for 2 h. The mixture was then filtered through a pad of Celite® and concentrated under reduced pressure. The residue was dissolved in methylene chloride, washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford methyl *N*-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]-*N*-methyl-L-valinate (0.49 g, 76%). ^{1}H NMR (400 MHz, CD_3OD) δ 0.85 (dd, 3 H), 1.06 (dd, 3 H), 2.35 (m, 1 H), 3.02 (d, 3 H), 3.75 (d, 3 H), 4.05 (d, 0.5 H), 4.78 (d, 0.5 H), 6.78 (d, 2 H), 7.42 (m, 4 H), 7.63 (d, 2 H); LC-MS *m/z* 341.2 (MH^+), retention time 2.37 minutes.

[175] Intermediate XIII-3: Methyl *N*-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]-L-valinate



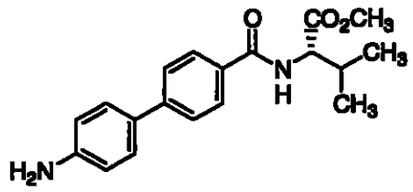
[176] Step 1. Preparation of methyl-*N*-[(4'-nitro-1,1'-biphenyl-4-yl)carbonyl]-L-valinate



[177] 4'-Nitro-1,1'-biphenyl-4-carboxylic acid (0.60 g, 2.4 mmol) was dissolved in methylene chloride (25 mL), and then oxalyl chloride (0.32 mL, 3.7 mmol) was added, followed by one drop of *N,N*-dimethylformamide. The resulting mixture was heated at 50°C for 1 h, concentrated under reduced pressure, and further dried under vacuum for 30 min. The residue was dissolved in

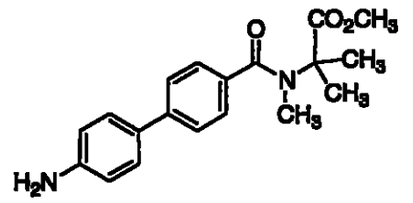
methylene chloride (20 mL) and added dropwise to an ice-cold mixture of methyl L-valinate hydrochloride (0.54 mg, 3.2 mmol), methylene chloride (25 mL), and triethylamine (1.74 mL, 12.3 mmol). The resulting solution was stirred on ice for 1 h and then at rt overnight. The mixture was diluted with methylene chloride and washed with 1*N* aqueous HCl solution and brine. The organic layer was separated and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage® system, 2:1 hexanes/EtOAc) to afford methyl-*N*-[(4'-nitro-1,1'-biphenyl-4-yl)carbonyl]-L-valinate (0.70 g, 80%). ^{1}H NMR (400 MHz, CD_3OD) δ 1.06 (dd, 6 H), 2.38 (m, 1 H), 3.77 (s, 3 H), 4.52 (d, 1 H), 7.82 (d, 2 H), 7.91 (d, 2 H), 7.97 (d, 2 H), 8.33 (d, 2 H); LC-MS *m/z* 357.1 (MH^+), retention time 3.07 minutes.

[178] Step 2. Preparation of methyl *N*-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]-L-valinate



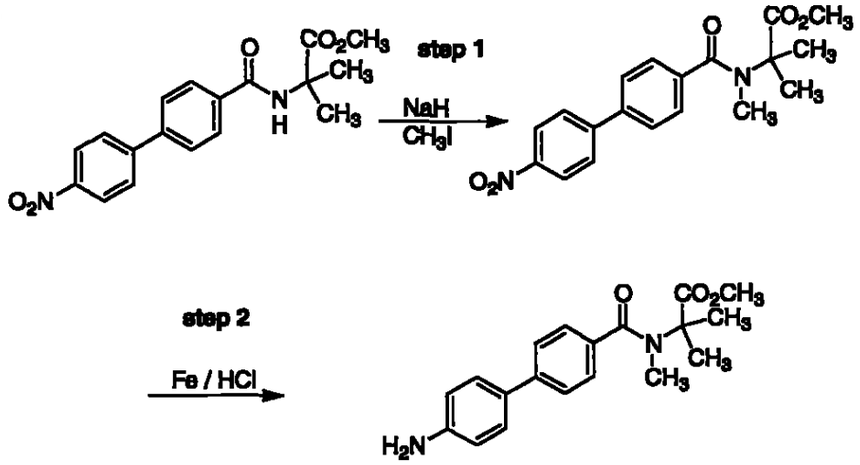
[179] To a solution of methyl-*N*-[(4'-nitro-1,1'-biphenyl-4-yl)carbonyl]-L-valinate (0.70 g, 1.9 mmol) in 85% ethanol (20 mL) was added iron powder (1.09 g, 19.6 mmol) and 2N aqueous HCl solution (1.0 mL). The resulting mixture was heated at reflux for 2 h. The mixture was then filtered through a pad of Celite® and concentrated under reduced preasure. The residue was dissolved in dichloromethane and washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford methyl *N*-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]-L-valinate (0.58 g, 90%). ^{1}H NMR (400 MHz, CD_3OD) δ 1.03 (dd, 6 H), 2.26 (m, 1 H), 3.74 (s, 3 H), 4.48 (d, 1 H), 6.77 (d, 2 H), 7.43 (d, 2 H), 7.62 (d, 2 H), 7.83 (d, 2 H); LC-MS *m/z* 327.1 (MH^+), retention time 2.27 minutes.

[180] **Intermediate XIII-4: Methyl *N*-[(4'-aminobiphenyl-4-yl)carbonyl]-N,2-dimethylalaninate**

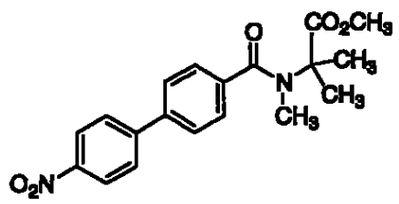


The preparation of methyl *N*-[(4'-aminobiphenyl-4-yl)carbonyl]-N,2-dimethylalaninate is described below in Reaction Scheme 11.

[181] **Reaction Scheme 11**

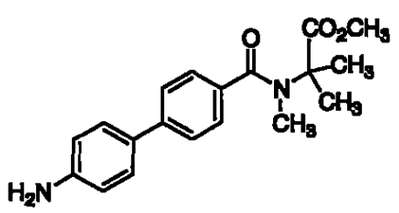


[182] Step 1. Preparation of methyl *N*,2-dimethyl-*N*-[(4'-nitrobiphenyl-4-yl)carbonyl]alaninate



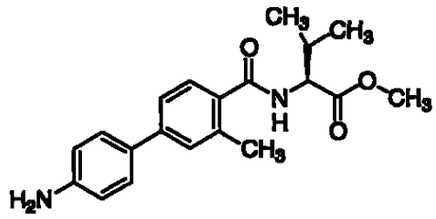
[183] As shown in Reaction Scheme 11, a mixture of methyl 2-methyl-*N*-[(4'-nitrobiphenyl-4-yl)carbonyl]alaninate (1.32 g, 3.9 mmol), sodium hydride (117 mg, 4.6 mmol), and *N,N*-dimethylformamide (15 mL) was stirred for 2 h at rt. Iodomethane (0.48 mL, 7.7 mmol) was added, and the reaction mixture was stirred overnight at rt. Water (30 mL) was added, and the mixture was extracted with ethyl acetate (2 x 10 mL). The combined extracts were evaporated to dryness, and crude product was purified by flash chromatography (Biotage®, 4:1 hexanes/EtOAc) to yield methyl *N*,2-dimethyl-*N*-[(4'-nitrobiphenyl-4-yl)carbonyl]alaninate as an off-white solid (1.29 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.47 (s, 6 H), 2.93 (s, 3 H), 3.58 (s, 3 H), 7.52 (d, 2 H), 7.84 (d, 2 H), 7.98 (d, 2 H), 8.30 (d, 2 H); LC-MS *m/z* 356.9 (MH^+), retention time 2.98 minutes.

[184] Step 2. Preparation of methyl *N*-[(4'-aminobiphenyl-4-yl)carbonyl]-N,2-dimethylalaninate

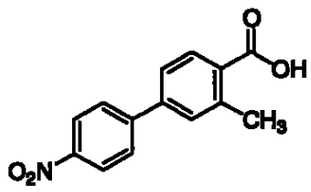


[185] As shown in Reaction Scheme 11, to a solution of methyl *N*,2-dimethyl-*N*-[(4'-nitrobiphenyl-4-yl)carbonyl]alaninate (1.92 g, 5.4 mmol) in 85% ethanol (50 mL) was added iron powder (3.01 g, 53.88 mmol) and 2 *M* aqueous HCl solution (2.69 mL, 5.4 mmol). The resulting mixture was heated at reflux for 2.5 h. The mixture was filtered through a pad of Celite® and concentrated under reduced pressure to afford methyl *N*-[(4'-aminobiphenyl-4-yl)carbonyl]-N,2-dimethylalaninate as a yellow solid (1.44 g, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.42 (s, 6 H), 2.94 (s, 3 H), 3.57 (s, 3 H), 5.30 (broad s, 2 H), 6.61 (d, 2 H), 7.31-7.40 (m, 4 H), 7.58 (d, 2 H); LC-MS *m/z* 327.2 (MH^+), retention time 1.84 minutes.

[186] Intermediate XIII-5: Methyl *N*-[(4'-amino-3-methylbiphenyl-4-yl)carbonyl]-L-valinate

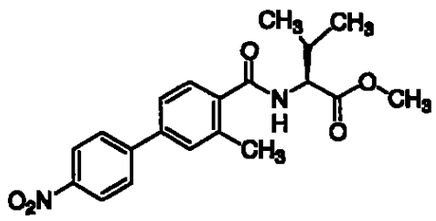


[187] Step 1. Preparation of 3-methyl-4'-nitrobiphenyl-4-carboxylic acid



[188] Methyl 3-methyl-4'-nitrobiphenyl-4-carboxylate (0.70 g, 2.1 mmol) was suspended in THF (5 mL), MeOH (5 mL) and water (2.5 mL), and NaOH (0.41 g, 10.3 mmol) was added. The reaction mixture was heated at 50°C for 3 h. Upon cooling to rt, the reaction mixture was concentrated in vacuo and purified by reversed-phase HPLC to give 0.498 g (94%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.62 (s, 3H), 7.62-7.68 (m, 2H), 7.91-8.05 (m 3H), 7.18 (t, 1H), 8.31 (d, 1H).

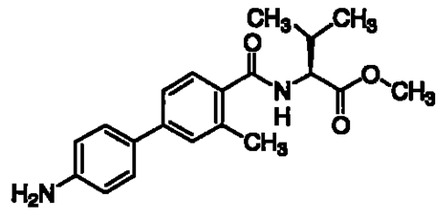
[189] Step 2. Preparation of methyl *N*-[(3-methyl-4'-nitrobiphenyl-4-yl)carbonyl]-L-valinate



[190] 3-Methyl-4'-nitrobiphenyl-4-carboxylic acid (0.50 g, 1.0 mmol) was dissolved in methylene chloride (10 mL), and then oxalyl chloride (0.25 mL, 0.29 mmol) was added, followed by one drop of DMF. The resulting mixture was stirred at 50°C for 45 min and then concentrated under reduced

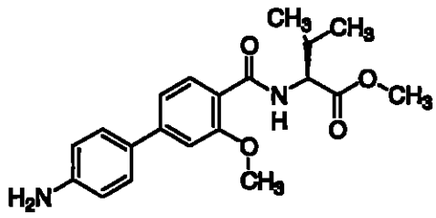
pressure. The residue was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cold mixture of L-valine methyl ester hydrochloride (0.39 g, 2.3 mmol), methylene chloride (10 mL), and triethylamine (1.08 mL, 7.75 mmol). The resulting solution was stirred at rt for 18 h. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (50% EtOAc in hexanes). This yielded 0.653 g (91%) of the title compound. LC/MS *m/z* 370.9 (MH^+), retention time 3.29 min. ^1H NMR (400 MHz, CD_2Cl_2) δ 1.06 (dd, 6H), 2.32-2.39 (m, 1H), 2.55 (s, 3H), 3.78 (s, 3H), 4.71-4.78 (m, 1H), 6.33 (d, 1H), 7.42-7.52 (m, 3H), 7.82 (d, 2H), 8.26 (d, 2H).

[191] Step 3. Preparation of methyl *N*-[(4'-amino-3-methylbiphenyl-4-yl)carbonyl]-L-valinate

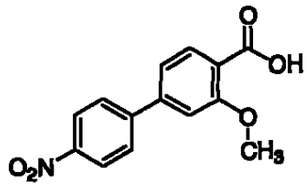


[192] Iron powder (0.79 g, 14 mmol) was added to a solution of methyl *N*-[(3-methyl-4'-nitrobiphenyl-4-yl)carbonyl]-L-valinate (0.65 g, 1.4 mmol) in ethanol (20 mL). Concentrated HCl (0.71 mL, 1.4 mmol) was added, and the mixture was heated at reflux for 1 h. Upon cooling to rt, the mixture was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. The material was purified by column chromatography (33% EtOAc in hexanes), yielding 0.50 g (quantitative) of the title compound. LC/MS *m/z* 341.1 (MH^+), retention time 2.19 min. ^1H NMR (400 MHz, CD_2Cl_2) δ 1.06 (dd, 6H), 2.32-2.39 (m, 1H), 2.50 (s, 3H), 3.78 (s, 3H), 4.71-4.78 (m, 1H), 6.33 (d, 1H), 6.78 (d, 2H), 7.38-7.44 (m, 5H).

[193] **Intermediate XIII-6: Methyl *N*-[(4'-amino-3-methoxybiphenyl-4-yl)carbonyl]-L-valinate**

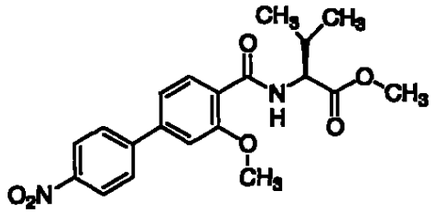


[194] Step 1. Preparation of 3-methoxy-4'-nitrobiphenyl-4-carboxylic acid



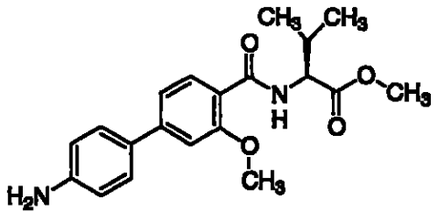
[195] Methyl 3-methoxy-4'-nitrobiphenyl-4-carboxylate (0.35 g, 0.97 mmol) was suspended in THF (6 mL), MeOH (6 mL) and water (3 mL), and NaOH (0.19 g, 4.9 mmol) was added. The reaction mixture was heated at 50°C for 3 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure and acidified with 2N HCl. The resulting solid was collected by filtration and dried in a 40°C vacuum oven, yielding 0.28 g (quantitative) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.90 (s, 3H), 7.35-7.41 (m, 2H), 7.77 (d, 1H), 8.03 (d, 2H), 8.36 (d, 2H).

[196] Step 2. Preparation of methyl *N*-[(3-methoxy-4'-nitrobiphenyl-4-yl)carbonyl]-L-valinate



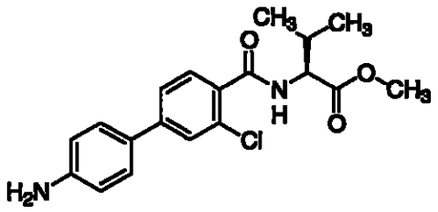
[197] 3-Methoxy-4'-nitrobiphenyl-4-carboxylic acid (0.28 g, 1.0 mmol) was dissolved in methylene chloride (10 mL), and then oxalyl chloride (0.13 mL, 1.51 mmol) was added, followed by one drop of DMF. The resulting mixture was stirred at 50°C for 45 min and then concentrated under reduced pressure. The residue was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cold mixture of L-valine methyl ester hydrochloride (0.21 g, 1.2 mmol), methylene chloride (10 mL), and triethylamine (0.57 mL, 4.1 mmol). The resulting solution was stirred at rt for 18 h. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (33% EtOAc in hexanes). LC/MS *m/z* 387.0 (MH^+), retention time 3.40 min. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.05 (t, 6H), 2.32-2.39 (m, 1H), 3.78 (s, 3H),4.10 (s, 3H), 4.71-4.78 (m, 1H), 7.22 (s, 1H), 7.38 (d, 1H), 7.80 (d, 2H), 8.22-8.37 (m, 4H).

[198] Step 3. Preparation of methyl *N*-[(4'-amino-3-methoxybiphenyl-4-yl)carbonyl]-L-valinate

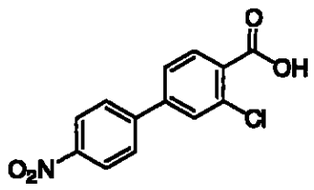


[199] Iron powder (0.35 g, 6.2 mmol) was added to a solution of methyl *N*-[(3-methoxy-4'-nitrobiphenyl-4-yl)carbonyl]-L-valinate (0.30 g, 0.62 mmol) in ethanol (10 mL). Concentrated HCl (0.31 mL, 0.62 mmol) was added, and the mixture was heated at reflux for 1 h. Upon cooling to rt, the mixture was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. The material was purified by column chromatography (33% EtOAc in hexanes), yielding 0.296 g (quantitative) of the title compound. *LC/MS m/z* 357.2 (MH^+), retention time 2.34 min.

[200] Intermediate XIII- 7: Methyl *N*-[(4'-amino-3-chlorobiphenyl-4-yl)carbonyl]-L-valinate

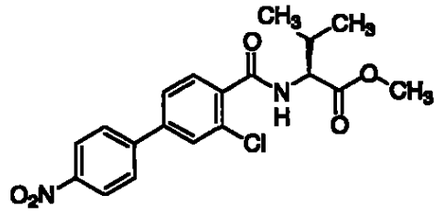


[201] Step 1. Preparation of 3-chloro-4'-nitrobiphenyl-4-carboxylic acid



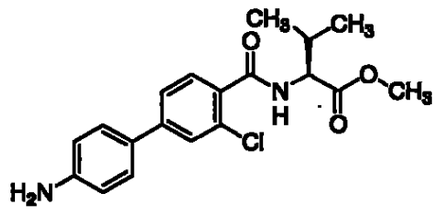
[202] Methyl 3-chloro-4'-nitrobiphenyl-4-carboxylate (0.50 g, 1.4 mmol) was suspended in THF (6 mL), MeOH (6 mL) and water (3 mL), and NaOH (0.27 g, 6.9 mmol) was added. The reaction mixture was heated at 50°C for 3 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure and acidified with 2N HCl. The resulting solid was collected by filtration and dried in a 40°C vacuum oven, yielding 0.315 g (83%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81-8.10 (m, 5H), 8.21-8.38 (m, 2H).

[203] Step 2. Preparation of methyl *N*-[(3-chloro-4'-nitrobiphenyl-4-yl)carbonyl]-L-valinate



[204] 3-Chloro-4'-nitrobiphenyl-4-carboxylic acid (0.31 g, 1.12 mmol) was dissolved in methylene chloride (10 mL), and then oxalyl chloride (0.15 mL, 1.7 mmol) was added, followed by one drop of DMF. The resulting mixture was stirred at 50°C for 45 min and then concentrated under reduced pressure. The residue was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cold mixture of L-valine methyl ester hydrochloride (0.22 g, 1.3 mmol), methylene chloride (10 mL), and triethylamine (0.62 mL, 4.5 mmol). The resulting solution was stirred at rt for 18 h and then concentrated under reduced pressure. The residue was taken up in EtOAc, passed through a plug of silica gel, and concentrated under reduced pressure. This yielded 0.305 g (70%) of the title compound. LC/MS *m/z* 390.9 (MH^+), retention time 3.30 min. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.06 (dd, 6H), 2.32-2.39 (m, 1H), 3.80 (s, 3H), 4.71-4.78 (m, 1H), 6.33 (d, 1H), 6.76 (d, 2H), 7.58-7.80 (m, 5H), 8.35 (d, 2H).

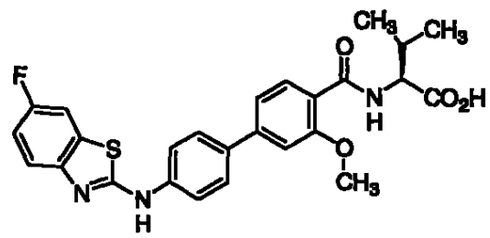
[205] Step 3. Preparation of methyl *N*-[(4'-amino-3-chlorobiphenyl-4-yl)carbonyl]-L-valinate



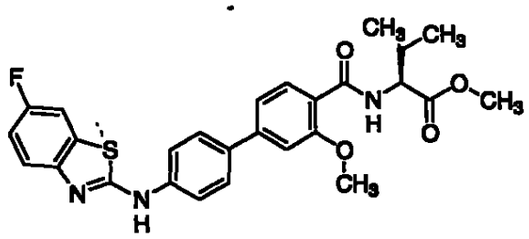
[206] Iron powder (0.44 g, 7.8 mmol) was added to a solution of methyl *N*-[(3-chloro-4'-nitrobiphenyl-4-yl)carbonyl]-L-valinate (0.30 g, 0.78 mmol) in ethanol (10 mL). Concentrated HCl (0.39 mL, 0.78 mmol) was added, and the mixture was heated at reflux for 3 h. Upon cooling to rt, the mixture was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. The material was purified by column chromatography (33% EtOAc in hexanes), yielding 0.25 g (89%) of the title compound. LC/MS *m/z* 361.2 (MH^+), retention time 2.36 min. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.06 (dd, 6H), 2.32-2.39 (m, 1H), 3.80 (s, 3H), 4.71-4.78 (m, 1H), 6.82 (d, 3H), 7.40-7.74 (m, 5H).

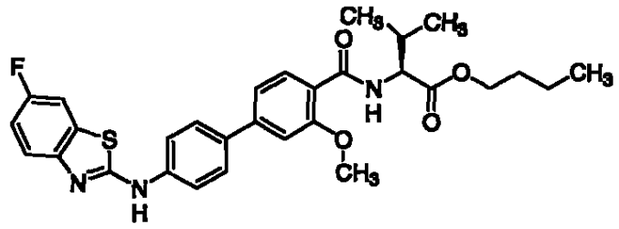
Preparation of Compounds of Formula (I) by Method C

[207] **Example 60: *N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine**



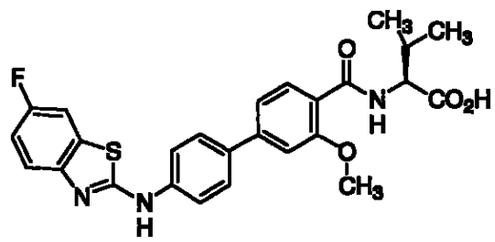
[208] Step 1. Preparation of methyl *N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valinate and butyl *N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valinate





[209] A mixture of methyl *N*-[(4'-amino-3-methoxybiphenyl-4-yl)carbonyl]-L-valinate (0.05 g, 0.14 mmol), 2-chloro-6-fluorobenzothiazole (0.03 g, 0.14 mmol), and 1-butanol (1.5 mL) was heated to 60-70°C, and then 4N HCl in 1,4-dioxane (0.02 mL, 0.07 mmol) was added with stirring. The reaction mixture was heated at 90°C for 18 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure and purified by HPLC (40-90% CH_3CN in H_2O/0.1% TFA gradient). This gave 7 mg (10%) of methyl *N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valinate and 39 mg (51%) of butyl *N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valinate.

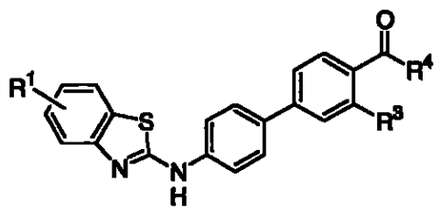
[210] Step 2. Preparation of *N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine



[211] Butyl *N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valinate (0.02 g, 0.03 mmol) was suspended in THF (1 mL), MeOH (1 mL) and water (0.5 mL), and then LiOH (0.01 g, 0.35 mmol) was added. The reaction mixture was heated at 50°C for 3 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure and acidified with 2N HCl. The resulting solid was collected by filtration and purified by HPLC (15-80% CH_3CN in H_2O/0.1% TFA gradient), yielding 19 mg (91%) of the title compound. LC/MS *m/z* 494.1 (MH^+), retention time 3.47 min. ^1H NMR (400 MHz, CD_3OD) δ 1.06 (d, 6H), 2.32-2.39 (m, 1H), 4.10 (s, 3H), 4.60 (d, 1H), 7.05 (t, 1H), 7.35-7.58 (m, 4H), 7.60 (d, 2H), 7.80 (d, 2H), 8.05 (d, 1H).

[212] By using the methods described above and by substituting the appropriate starting materials, compounds of Formula (I), listed in Table 3a below, were similarly prepared.

[213] Table 3a. Preparative Examples of Compounds of Formula (I) by Method C



Example No.	R^1	R^3	R^4	LC-MS Ret. Time (min)	LC-MS $[M+H]^+$
60	6-F	OCH_3	L-Val-OH	3.50	494.1
61	6-F	CH_3	L-Val-OH	3.39	478.2
62	6-OCH_3	CH_3	L-Val-OH	3.21	490.2
63	H	CH_3	L-Val-OH	3.24	460.2
64	6-i-Pr	CH_3	L-Val-OH	3.65	502.2
65	6-Cl	CH_3	L-Val-OH	3.59	494.2

Example No.	R^1	R^3	R^4	LC-MS Ret. Time (min)	LC-MS $[M+H]^+$
66	7-F	CH_3	L-Val-OH	3.47	478.2
67	7-Cl	CH_3	L-Val-OH	3.62	494.2
68	H	OCH_3	L-Val-OH	3.37	476.1
69	H	H	L-Val-OH	3.39	446.2
70	H	H	D-Val-OH	3.21	446.2
71	6-Cl	OCH_3	L-Val-OH	3.71	510.2
72	7-F	OCH_3	L-Val-OH	3.56	494.2
73	7-Cl	OCH_3	L-Val-OH	3.71	510.1
74	6-i-Pr	OCH_3	L-Val-OH	3.77	518.2
75	H	Cl	L-Val-OH	3.36	480.2
76	6-i-Pr	Cl	L-Val-OH	3.73	522.2
77	6-Cl	Cl	L-Val-OH	3.67	550.9
78	7-F	Cl	L-Val-OH	3.53	498.1
79	7-Cl	Cl	L-Val-OH	3.68	514.1
80	H	OCH_3	L-Leu-OH	3.87	490.3
81	6- OCH_3	OCH_3	L-Leu-OH	3.85	520.3
82	6-Cl	OCH_3	L-Leu-OH	4.19	524.3
83	4-Cl, 6-F	OCH_3	L-Leu-OH	4.21	542.1
84	6-NO_2	OCH_3	L-Leu-OH	3.98	535.0
85	6-$(CH_3)SO_2$	OCH_3	L-Leu-OH	3.54	568.2
86	6-i-Pr	OCH_3	L-Leu-OH	4.24	532.3

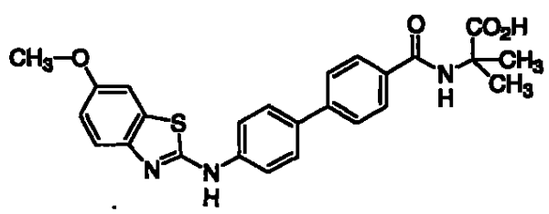
[214] **Table 3b. IUPAC Names of Compounds in Table 3a**

Example No.	IUPAC Name
60	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine
61	*N*-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine

Example No.	IUPAC Name
62	*N*-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine
63	*N*-{[4'-(1,3-benzothiazol-2-ylamino)-3-methylbiphenyl-4-yl]carbonyl}-L-valine
64	*N*-({4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine
65	*N*-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine
66	*N*-({4'-[(7-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine
67	*N*-({4'-[(7-chloro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine
68	*N*-{[4'-(1,3-benzothiazol-2-ylamino)-3-methoxybiphenyl-4-yl]carbonyl}-L-valine
69	*N*-{[4'-(1,3-benzothiazol-2-ylamino)biphenyl-4-yl]carbonyl}-L-valine
70	*N*-{[4'-(1,3-benzothiazol-2-ylamino)biphenyl-4-yl]carbonyl}-D-valine
71	*N*-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine
72	*N*-({4'-[(7-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine
73	*N*-({4'-[(7-chloro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine
74	*N*-({4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine
75	*N*-{[4'-(1,3-benzothiazol-2-ylamino)-3-chlorobiphenyl-4-yl]carbonyl}-L-valine
76	*N*-({3-chloro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine
77	*N*-({3-chloro-4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine
78	*N*-({3-chloro-4'-[(7-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine
79	*N*-({3-chloro-4'-[(7-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine
80	*N*-{[4'-(1,3-benzothiazol-2-ylamino)-3-methoxybiphenyl-4-yl]carbonyl}-L-leucine
81	*N*-({3-methoxy-4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine

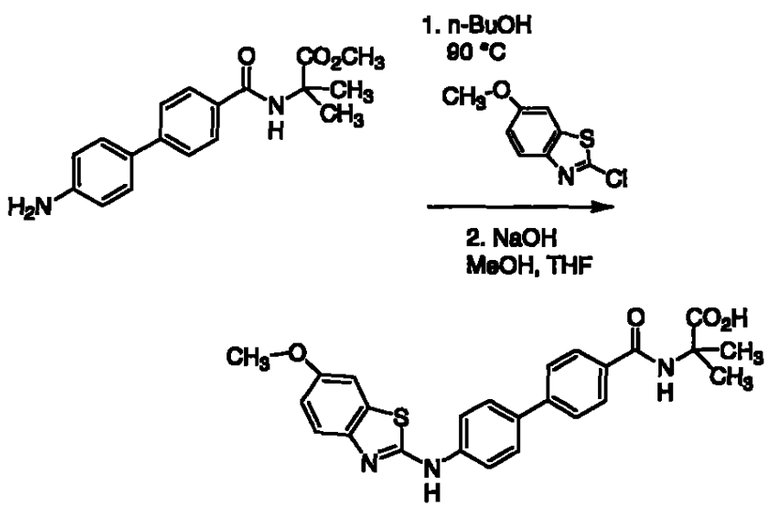
Example No.	IUPAC Name
82	*N*-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-leucine
83	*N*-({4'-[(4-chloro-6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-leucine
84	*N*-({3-methoxy-4'-[(6-nitro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine
85	*N*-[(3-methoxy-4'-{[6-(methylsulfonyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-leucine
86	*N*-({4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-leucine

[215] **Example 87: *N*-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine**



The preparation of *N*-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine is described below in Reaction Scheme 12.

[216] **Reaction Scheme 12**

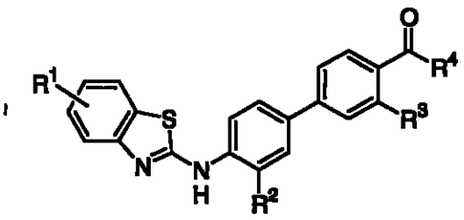


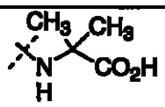
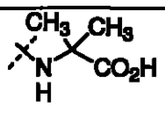
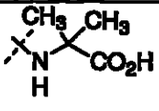
[217] As shown in Reaction Scheme 12, a mixture of methyl *N*-[(4'-aminobiphenyl-4-yl)carbonyl]-2-methylalaninate (100 mg, 0.32 mmol), 2-chloro-6-methoxybenzothiazole (83 mg, 0.42 mmol, commercially available), and 1-butanol (4.0 mL) was heated at 90°C overnight. The solvent was evaporated under reduced pressure to afford crude methyl *N*-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalaninate; LC-MS *m/z* 476.2 (MH^+), retention time 3.25 minutes.

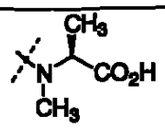
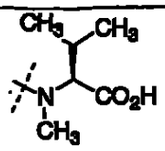
[218] The intermediate aminobenzothiazole was dissolved in methanol (0.4 mL) and tetrahydrofuran (0.4 mL). Aqueous NaOH solution (2*N*, 0.64 mL, 1.28 mmol) was added, and the mixture was stirred at rt overnight. The mixture was filtered and the filtrate was purified by preparative reverse-phase HPLC (water/acetonitrile gradient, containing 0.1% TFA) to give *N*-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine (58 mg, 39%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.47 (s, 6 H), 3.78 (s, 3 H), 6.95 (d, 1 H), 7.24 (s, 1 H), 7.32 (d, 1 H), 7.72-7.78 (m, 4 H), 7.88 (d, 2 H), 7.92 (d, 2 H), 8.47 (s, 1 H), 10.27 (s, 1 H); LC-MS *m/z* 462.5 (MH^+), retention time 2.94 minutes.

[219] By using the methods described above and by substituting the appropriate starting materials, compounds of Formula (I), listed in Table 4a below, were similarly prepared.

[220] **Table 4a. Preparative Examples of Compounds of Formula (I) by Method C**



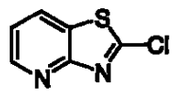
Example No.	R^1	R^2	R^3	R^4	LC-MS retention time (min)	LC-MS $[M+H]^+$
87	6-OMe	H	H		2.94	462.4
88	H	H	H		2.98	432.2
89	6-Cl	H	H		3.31	466.5

Example No.	R^1	R^2	R^3	R^4	LC-MS retention time (min)	LC-MS $[M+H]^+$
90	H	H	H		3.09	432.2
91	H	H	H		3.33	460.2

[221] **Table 4b. IUPAC Names of Compounds in Table 4a**

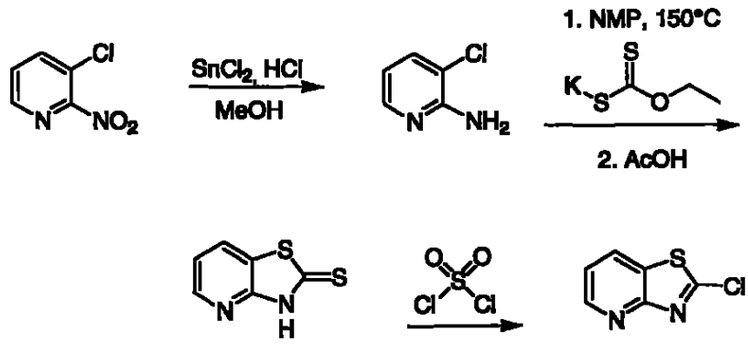
Example No.	IUPAC Name
87	*N*-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine
88	*N*-{[4'-(1,3-benzothiazol-2-ylamino)biphenyl-4-yl]carbonyl}-2-methylalanine
89	*N*-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine
90	*N*-{[4'-(1,3-benzothiazol-2-ylamino)biphenyl-4-yl]carbonyl}-*N*-methyl-L-alanine
91	*N*-{[4'-(1,3-benzothiazol-2-ylamino)biphenyl-4-yl]carbonyl}-*N*-methyl-L-valine

[222] **Preparation of Intermediate V-1: 2-chloro[1,3]thiazolo[4,5-b]pyridine**

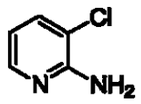


The preparation of 2-chloro[1,3]thiazolo[4,5-b]pyridine is described below in Reaction Scheme 13.

[223] **Reaction Scheme 13**

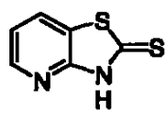


[224] Step 1: Preparation of 2-amino-3-chloropyridine



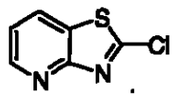
[225] A sample of 3-chloro-2-nitropyridine (1.00 g, 6.31 mmol) was dissolved in methanol (10 mL), treated with Tin(II) chloride (5.98 g, 31.54 mmol) followed by concentrated HCl (2.63 mL, 31.54 mmol). The reaction mixture was allowed to stir overnight at rt. The solution was then diluted with ethyl acetate and washed with 1N NaOH solution. The organic phase was then washed with concentrated $NaHCO_3$ solution and dried over Na_2SO_4. Concentration in vacuo gave the title compound (510.0mg, 63%). ^{1}H NMR (400 MHz, CD_3CN) δ 6.80 (m, 1 H), 7.60 (d, 1 H), 8.12 (d, 1 H).

[226] Step 2: Preparation of [1,3]thiazolo[4,5-b]pyridine-2(3H)-thione



[227] The intermediate 2-amino-3-chloro-pyridine (510 mg, 3.97 mmol) was dissolved in 1-methyl-2-pyrrolidinone (7 mL) and treated with potassium ethyl xanthate (953.9 mg, 5.95 mmol). The solution was heated to 150°C overnight. The solution was then cooled to rt and treated with glacial acetic acid (1 mL) and diluted with water (150 ml). The resulting precipitate was filtered off and triturated with 1:1 water/ethanol solution. The filter cake was then suspended in EtOAc. Concentration in vacuo gave the title compound (650.0 mg, 97%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25 (m, 1 H), 8.11 (d, 1 H), 8.35 (d, 1 H).

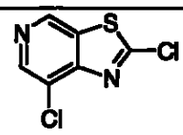
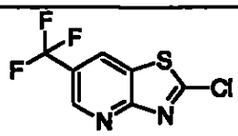
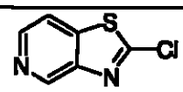
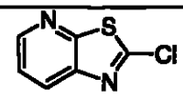
[228] Step 3: Preparation of 2-chloro[1,3]thiazolo[4,5-b]pyridine



[229] The intermediate [1,3]thiazolo[4,5-b]pyridine-2(3H)-thione (644.0 mg, 3.83 mmol, dry powder) was treated with neat sulfuryl chloride (3.08 ml, 38.28 mmol) and allowed to stir at rt overnight. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with 1N NaOH, followed by brine, and dried over Na_2SO_4. Concentration in vacuo gave the title compound (260.0 mg, 40%). LC/MS *m/z* 171.2 (MH^+); retention time 1.55min. ^1H NMR (400 MHz, DMSO-d_6) δ 7.58 (m, 1 H), 8.62 (d, 1 H), 8.78 (d, 1 H).

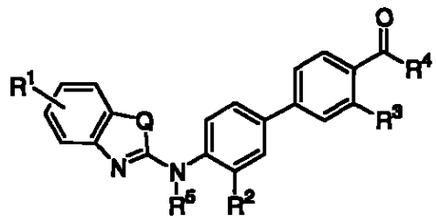
[230] The following intermediates of Formula (V) were prepared using the above method and the appropriate commercially available, chloro-nitro-pyridine as the starting material.

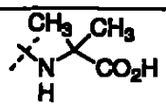
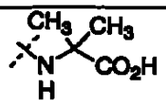
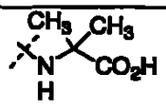
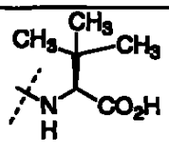
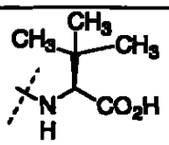
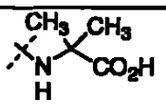
[231] Table 5. Examples of Compounds of Formula (V)

Example	Structure	LC/MS *m/z* (MH^+)	Ret. Time (min)
Intermediate V-2		205.2	2.24
Intermediate V-3		239.4	2.64
Intermediate V-4		171.2	1.15
Intermediate V-5		171.2	2.13

[232] By using the methods described in the procedures provided herein and by substituting the appropriate starting materials, compounds of Formula (I), listed in Table 6, may be similarly prepared.

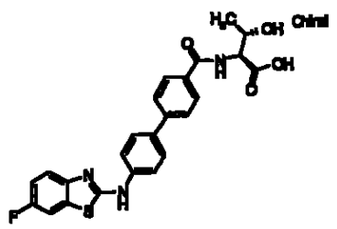
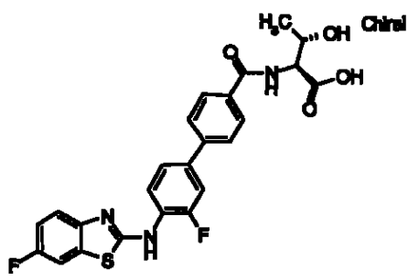
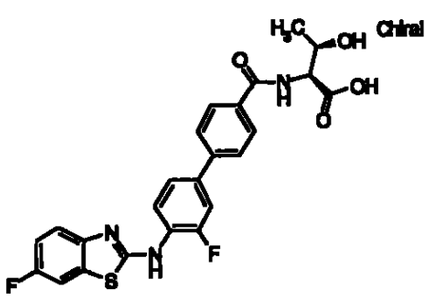
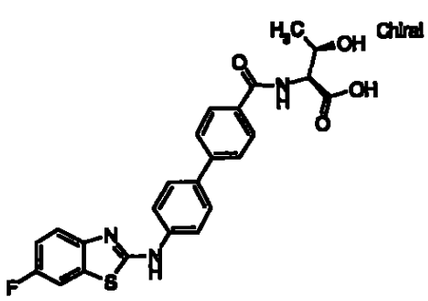
[233] **Table 6. Examples of Compounds of Formula (I)**

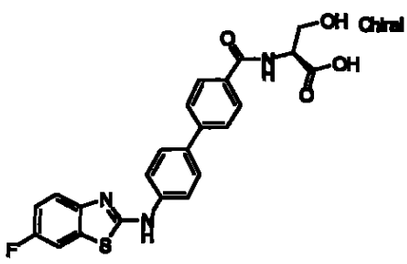
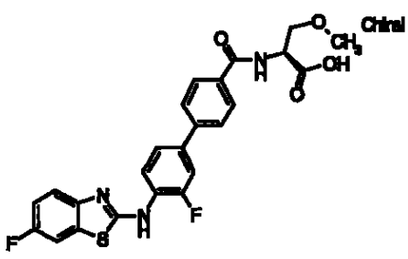
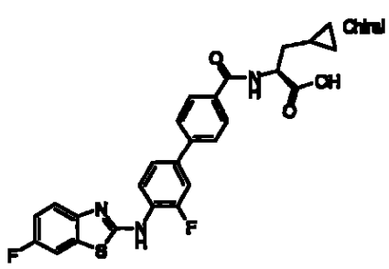
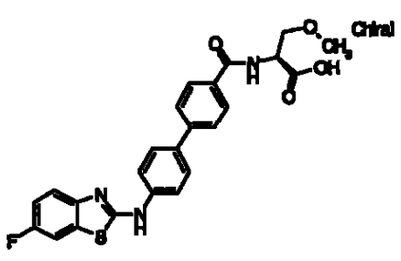
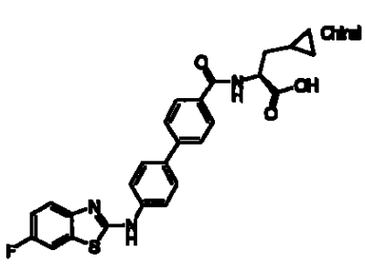


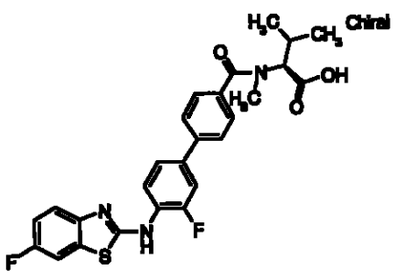
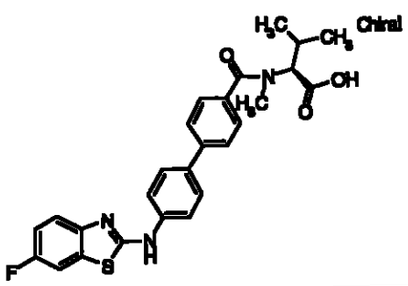
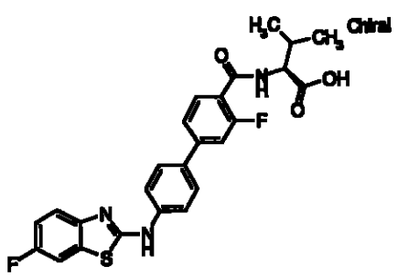
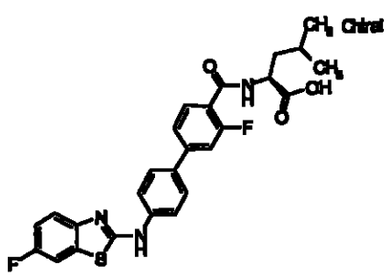
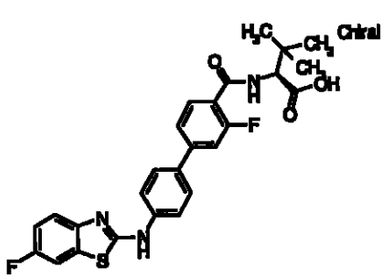
Example No.	Q	R^1	R^2	R^3	R^4	R^5
92	NH	H	H	H		H
93	NH	6-F	F	H		H
94	O	6-F	F	H		H
95	S	6-OMe	H	CH_3		CH_3
96	O	6-CF_3	F	H	L-Leu-OH	CH_3
97	O	5-CH_3	F	H	L-Val-OH	CH_3
98	O	5-Cl	H	Cl		CH_3
99	S	6-F	F	H		CH_2CH_3 OH

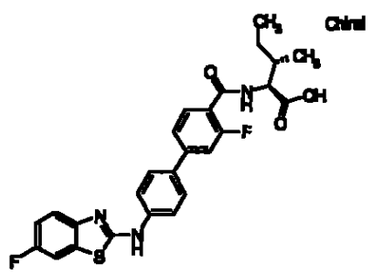
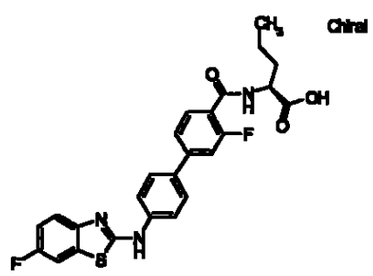
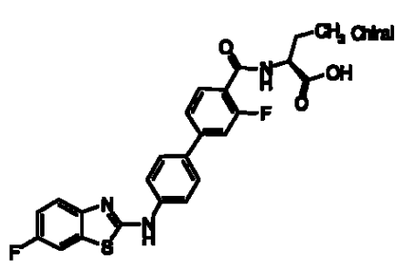
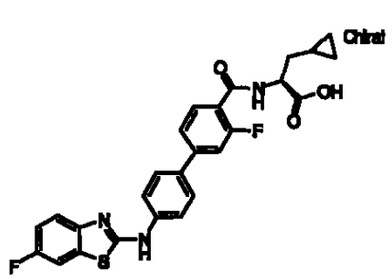
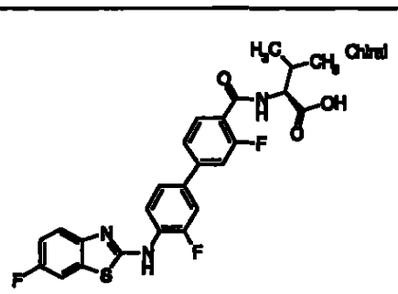
[234] By using the methods described in the procedures provided herein and by substituting the appropriate starting materials, compounds of Formula (I), listed in Table 7, were prepared.

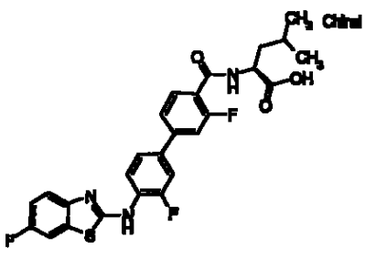
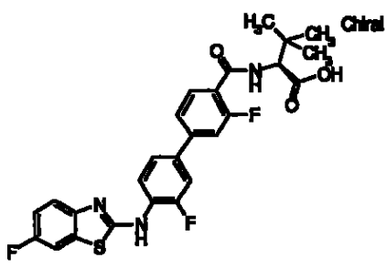
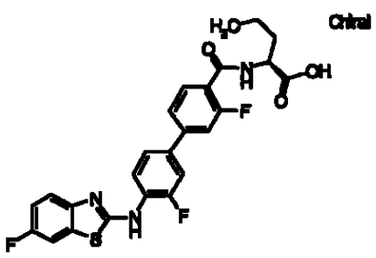
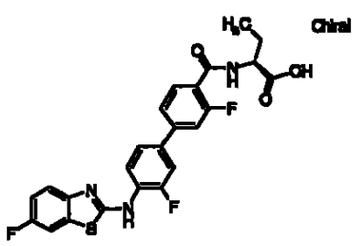
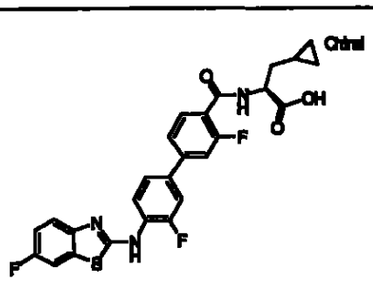
[235] **Table 7a. Examples of Compounds**

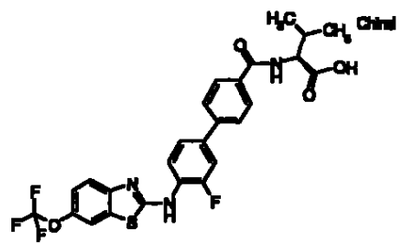
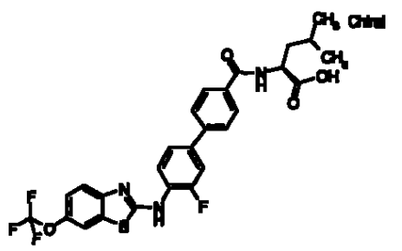
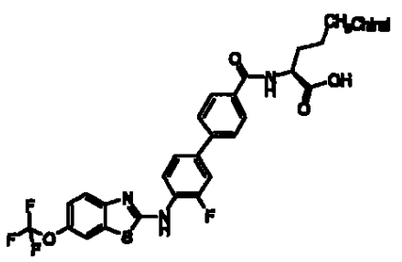
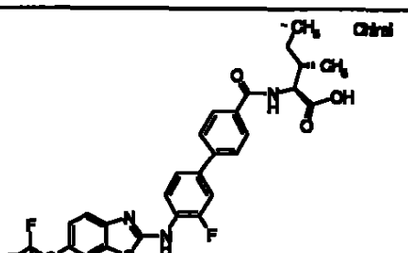
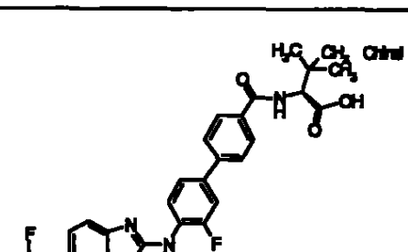
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
100		2.97	466.1	A
101		3.04	484.1	A
102		3.03	484.1	A
103		2.97	466.1	A

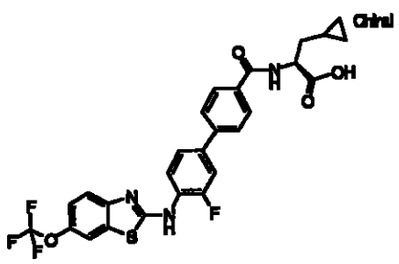
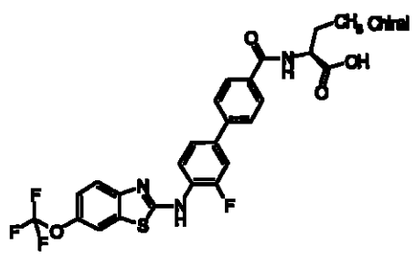
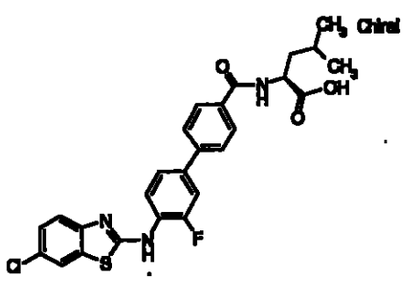
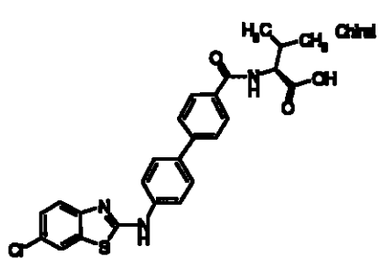
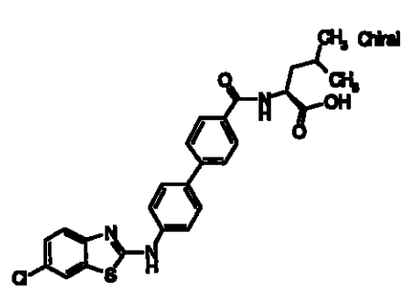
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
104		2.88	452.1	A
105		3.19	484.1	A
106		3.48	494.1	A
107		3.14	466.1	A
108		3.41	476.2	A

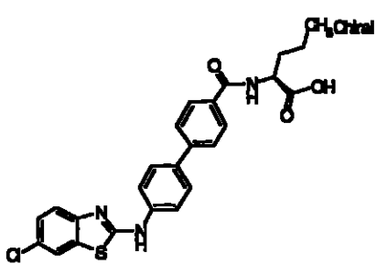
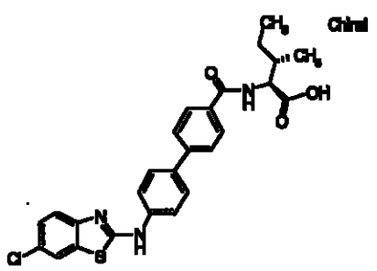
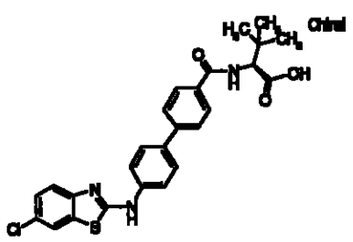
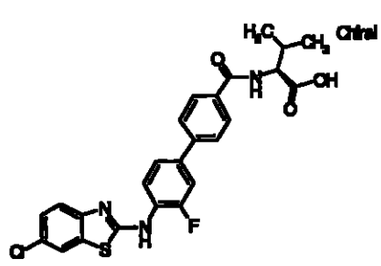
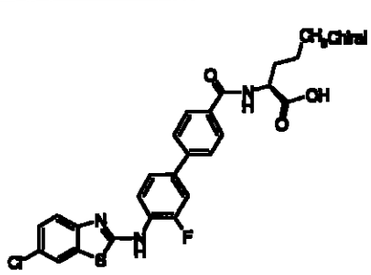
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
109		3.53	496.1	A
110		3.43	478.2	A
111		3.52	482.2	A
112		3.66	496.2	A
113		3.66	496.2	A

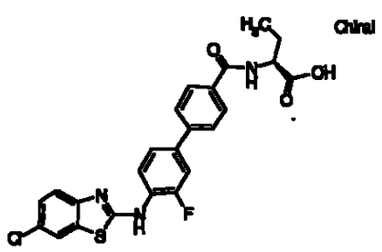
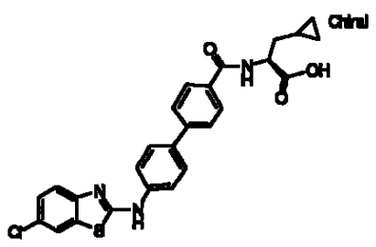
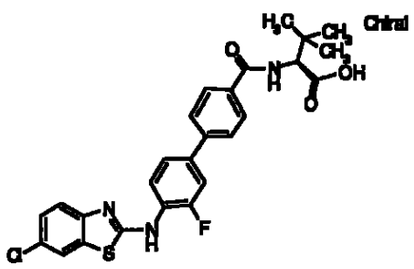
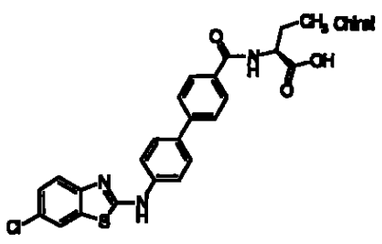
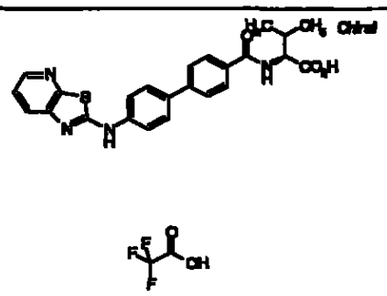
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
114		3.67	496.2	A
115		3.53	482.2	A
116		3.39	468.2	A
117		3.56	494.2	A
118		3.6	500.2	A

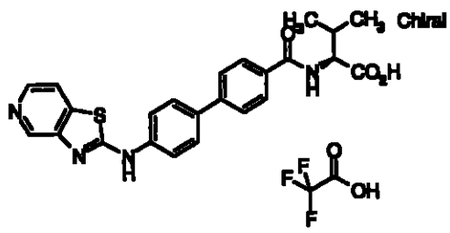
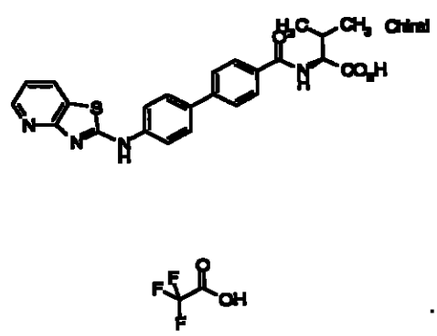
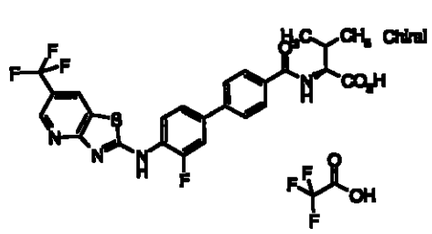
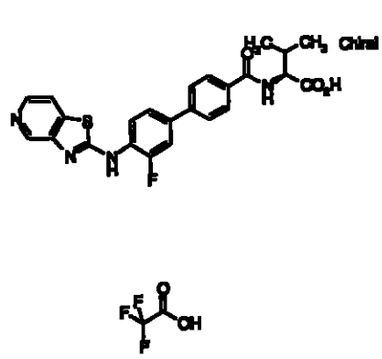
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
119		3.72	514.2	A
120		3.74	514.2	A
121		3.61	500.1	A
122		3.47	485.1	A
123		3.64	512.1	A

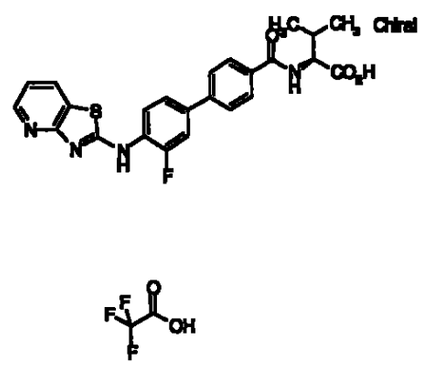
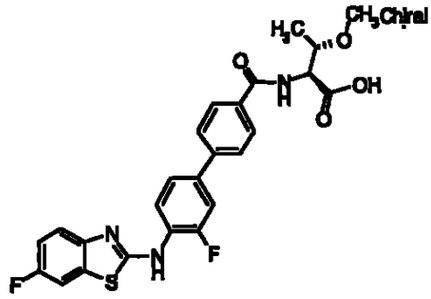
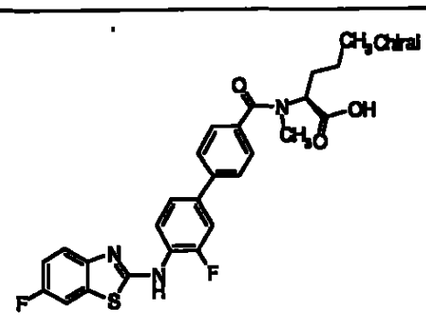
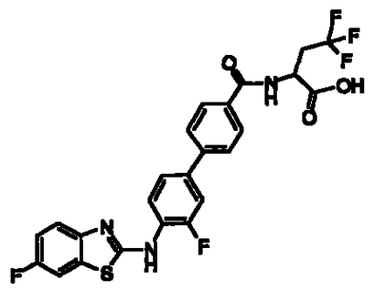
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
124		4.27	548.2	A
125		4.56	562.2	A
126		4.23	562.1	A
127		4.56	562.1	A
128		4.45	562.2	A

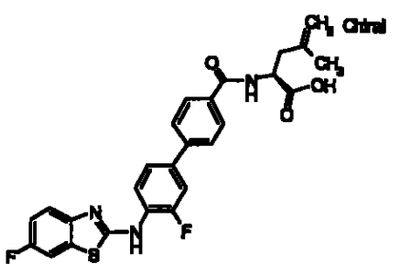
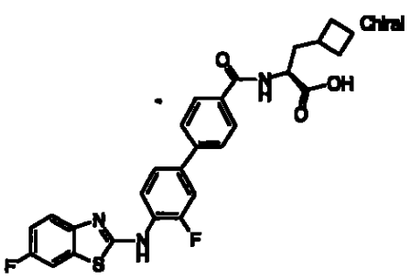
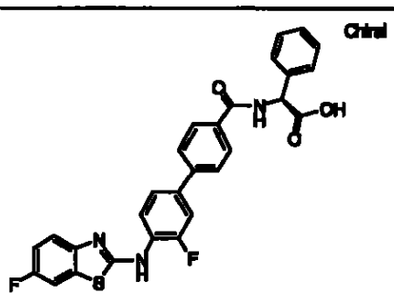
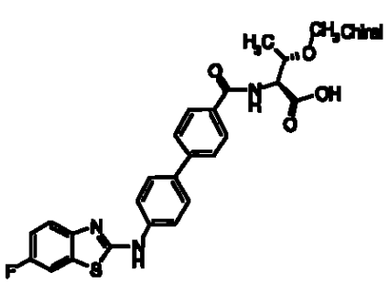
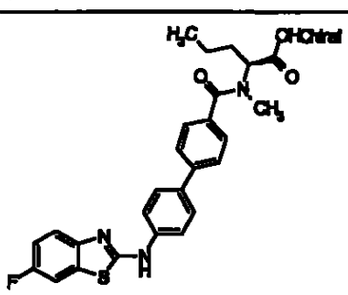
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
129		4.47	560.2	A
130		4.28	534.1	A
131		3.79	512.1	A
132		3.57	480.1	A
133		3.71	494.1	A

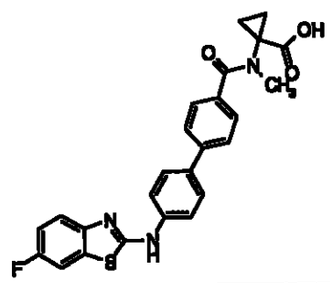
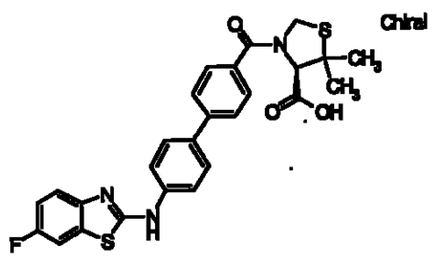
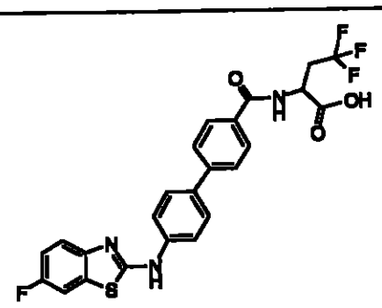
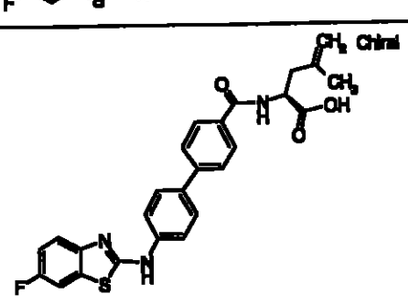
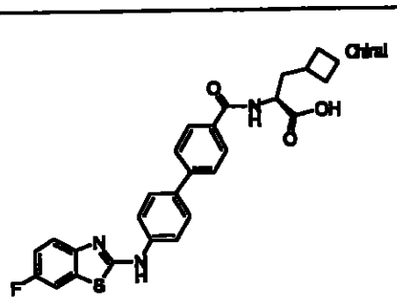
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
134		3.59	480.1	A
135		3.71	494.1	A
136		3.7	494.1	A
137		3.63	498.1	A
138		3.65	498.1	A

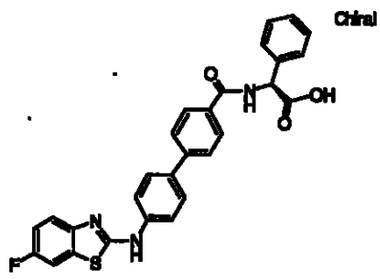
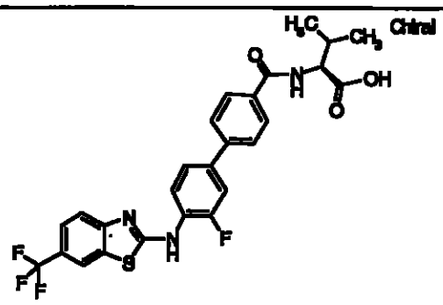
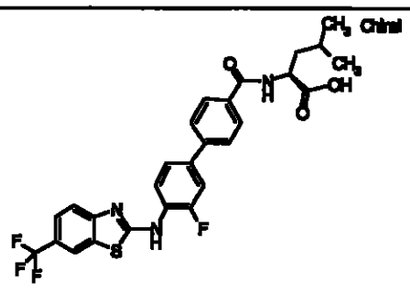
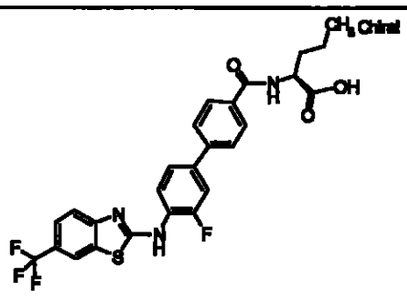
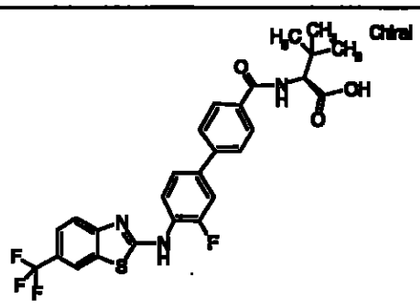
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
139		3.51	484.1	A
140		3.61	492.1	A
141		3.78	512.1	A
142		3.44	466.1	A
143		2.95	447.2	C

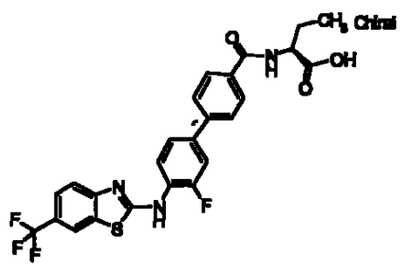
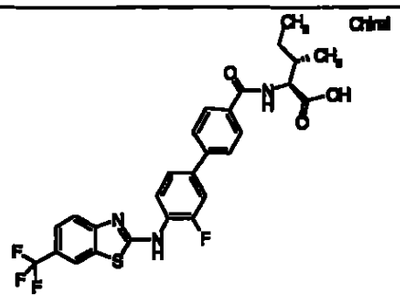
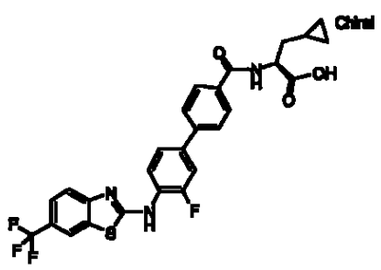
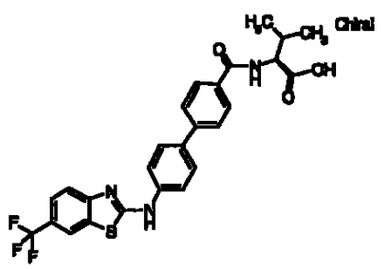
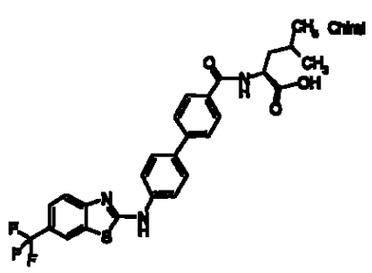
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
144		2.23	447.2	C
145		2.35	447.2	C
146		3.32	533.2	C
147		2.25	465.2	C

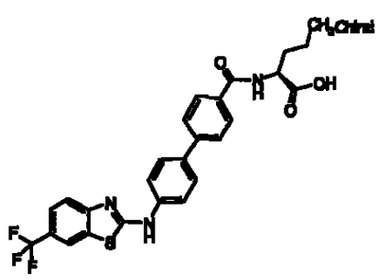
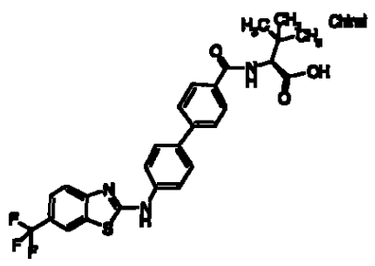
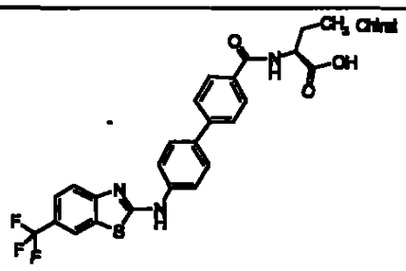
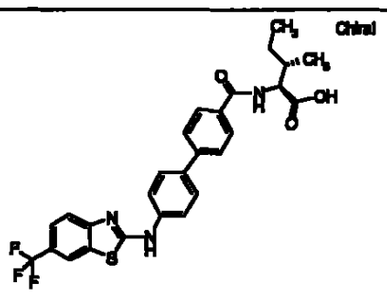
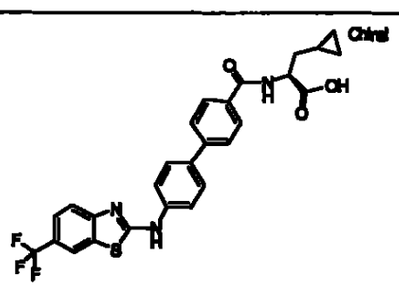
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
148		2.42	465.2	C
149		3.27	498.1	A
150		3.53	496.1	A
151		3.49	522.2	A

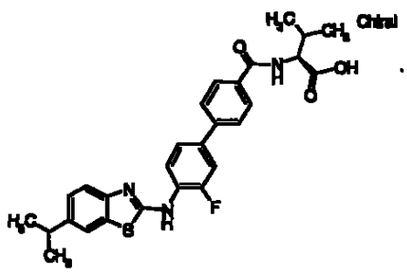
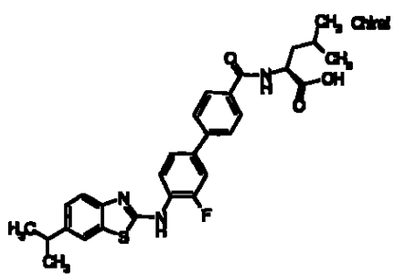
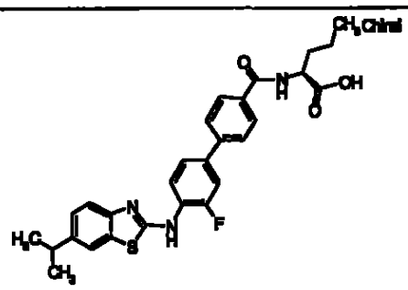
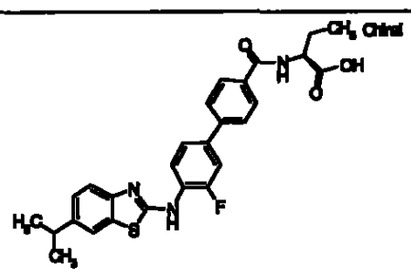
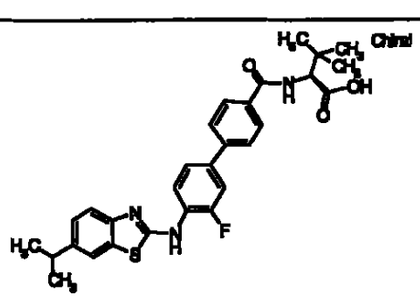
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
152		3.51	494.1	A
153		3.67	508.2	A
154		3.54	516.1	A
155		3.24	480.2	A
156		3.46	478.2	A

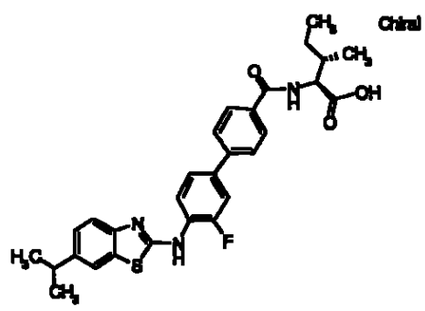
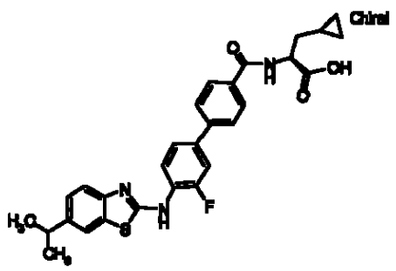
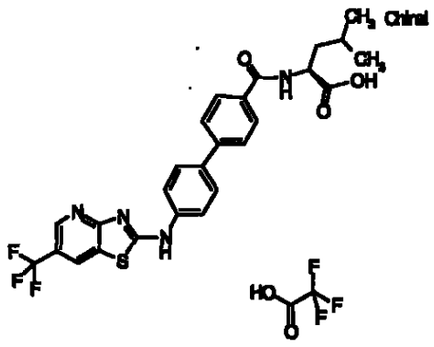
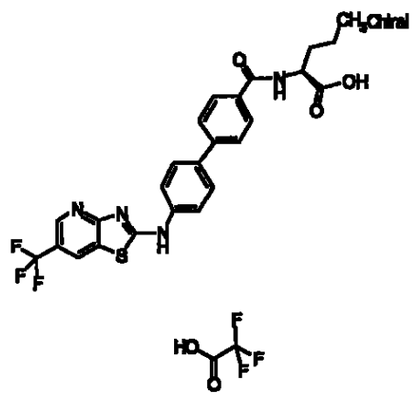
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
157		3.16	462.1	A
158		3.55	508.1	A
159		3.41	504.1	A
160		3.42	476.2	A
161		3.59	490.2	A

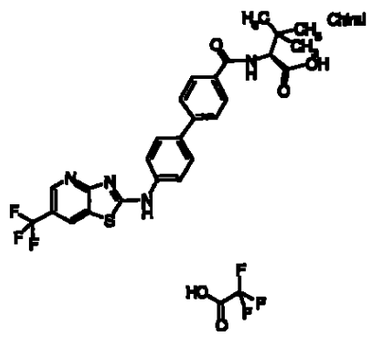
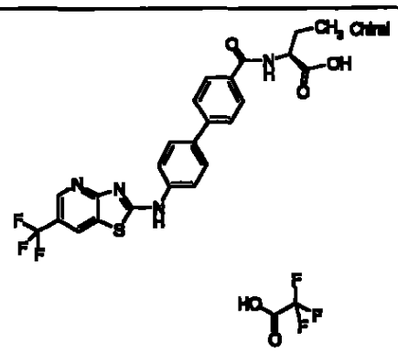
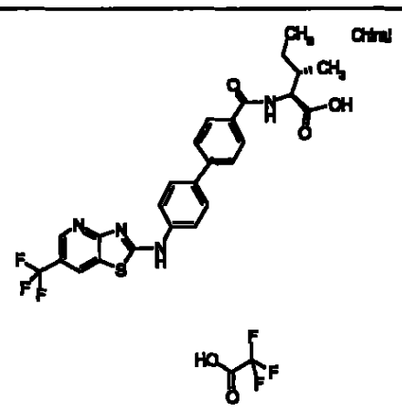
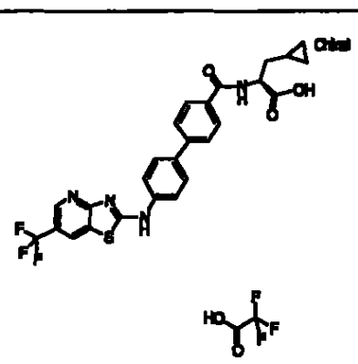
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
162		3.47	498.2	A
163		3.72	532.2	A
164		3.87	546.2	A
165		3.74	532.2	A
166		3.84	546.2	A

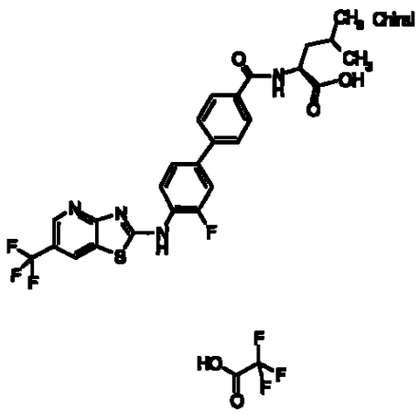
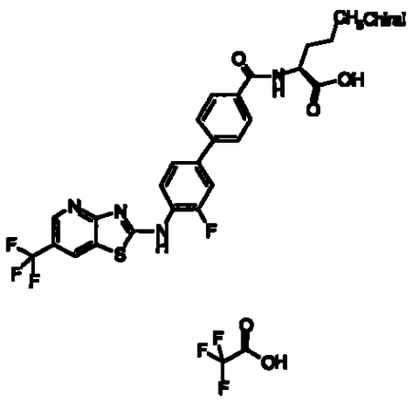
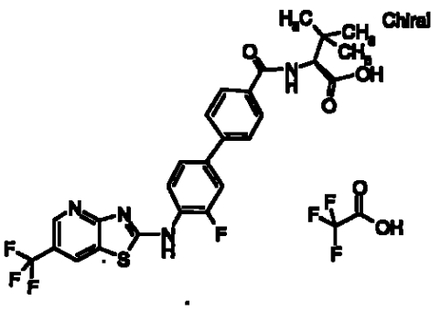
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
167		3.6	518.2	A
168		3.86	546.2	A
169		3.74	544.2	A
170		3.66	514.2	A
171		3.79	528.2	A

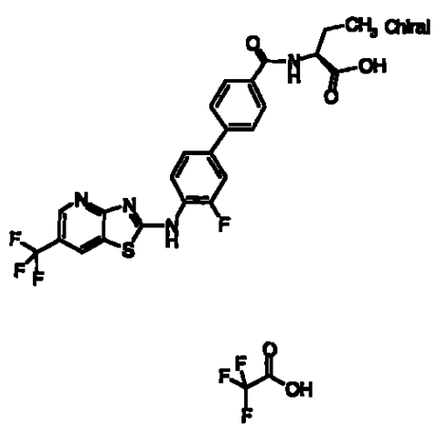
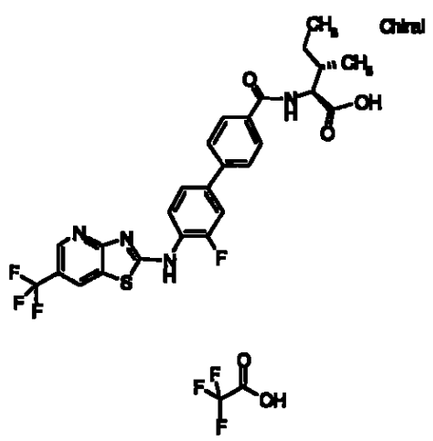
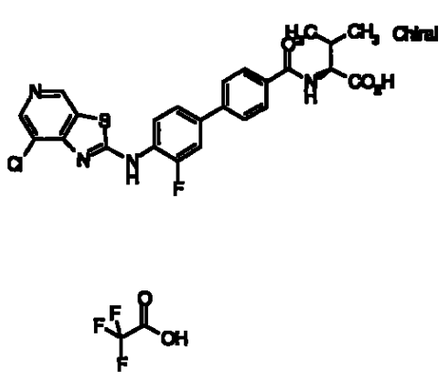
Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
172		3.68	514.2	A
173		3.77	528.2	A
174		3.54	500.2	A
175		3.78	528.2	A
176		3.68	526.2	A

Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
177		3.74	506.2	A
178		3.88	520.2	A
179		3.75	506.2	A
180		3.62	492.2	A
181		3.87	520.2	A

Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
182		3.87	520.2	A
183		3.77	518.2	A
184		3.37	529.2	A
185		3.23	515.2	A

Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
186		3.35	529.2	A
187		3.11	501.2	A
188		3.35	529.2	A
189		3.25	527.2	A

Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
190		3.43	547.2	A
191		3.3	533.2	A
192		3.4	547.2	A

Example No.	Structure	LC-MS Ret. Time (min)	LC-MS [M+H]+	Method
193		3.17	519.2	A
194		3.42	547.2	A
195		2.7	499.1	C

[236] **Table 7b. IUPAC Names of Compounds in Table 7a**

Example No.	IUPAC Name
100	N-({4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-allothreonine
101	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-allothreonine
102	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-threonine
103	N-({4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-threonine
104	N-({4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-serine
105	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-O-methyl-L-serine
106	3-Cyclopropyl-N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine
107	N-({4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-O-methyl-L-serine
108	3-Cyclopropyl-N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine
109	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-N-methyl-L-valine
110	N-({4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-N-methyl-L-valine
111	N-({3-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine
112	N-({3-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine
113	N-({3-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-methyl-L-valine
114	N-({3-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-isoleucine
115	N-({3-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-norvaline
116	(2S)-2-[({3-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid
117	3-Cyclopropyl-N-({3-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine
118	N-({3,3'-Difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine
119	N-({3,3'-Difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine
120	N-({3,3'-Difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-methyl-L-valine
121	N-({3,3'-Difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-norvaline
122	(2S)-2-[({3,3'-Difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid

Example No.	IUPAC Name
123	3-Cyclopropyl-N-({3,3'-difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine
124	N-[(3'-Fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-valine
125	N-[(3'-Fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-leucine
126	N-[(3'-Fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-norvaline
127	N-[(3'-Fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-isoleucine
128	N-[(3'-Fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-3-methyl-L-valine
129	3-Cyclopropyl-N-[(3'-fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-alanine
130	(2S)-2-{[(3'-Fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]amino}butanoic acid
131	N-({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]-3'-fluorobiphenyl-4-yl}carbonyl)-L-leucine
132	N-({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine
133	N-({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine
134	N-({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-norvaline
135	N-({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-isoleucine
136	N-({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-methyl-L-valine
137	N-({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]-3'-fluorobiphenyl-4-yl}carbonyl)-L-valine
138	N-({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]-3'-fluorobiphenyl-4-yl}carbonyl)-L-norvaline
139	(2S)-2-[({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]-3'-fluorobiphenyl-4-yl}carbonyl)amino]butanoic acid
140	N-({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-cyclopropyl-L-alanine
141	N-({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]-3'-fluorobiphenyl-4-yl}carbonyl)-3-methyl-L-valine
142	(2S)-2-[({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid
143	N-{[4'-([1,3]Thiazolo[5,4-b]pyridin-2-ylamino)biphenyl-4-yl]carbonyl}-L-valine trifluoroacetate
144	N-{[4'-([1,3]Thiazolo[4,5-c]pyridin-2-ylamino)biphenyl-4-yl]carbonyl}-L-valine trifluoroacetate
145	N-{[4'-([1,3]Thiazolo[4,5-b]pyridin-2-ylamino)biphenyl-4-yl]carbonyl}-L-valine trifluoroacetate
146	N-[(3'-Fluoro-4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-valine trifluoroacetate

Example No.	IUPAC Name
147	N-{[3'-Fluoro-4'-([1,3]thiazolo[4,5-c]pyridin-2-ylamino)biphenyl-4-yl]carbonyl}-L-valine trifluoroacetate
148	N-{[3'-Fluoro-4'-([1,3]thiazolo[4,5-b]pyridin-2-ylamino)biphenyl-4-yl]carbonyl}-L-valine trifluoroacetate
149	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-O-methyl-L-allothreonine
150	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-N-methyl-L-norvaline
151	4,4,4-Trifluoro-2-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid
152	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-4-methylene-L-norvaline
153	3-Cyclobutyl-N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine
154	(2S)-[({3'-Fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino](phenyl)acetic acid
155	N-({4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-O-methyl-L-allothreonine
156	N-({4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-N-methyl-L-norvaline
157	1-[({4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)(methyl)amino]cyclopropanecarboxylic acid
158	(4R)-3-({4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid
159	4,4,4-Trifluoro-2-[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid
160	N-({4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-4-methylene-L-norvaline
161	3-Cyclobutyl-N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine
162	(2S)-[({4'-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino](phenyl)acetic acid
163	N-[(3'-Fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-valine
164	N-[(3'-Fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-leucine
165	N-[(3'-Fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-norvaline
166	N-[(3'-Fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-3-methyl-L-valine
167	(2S)-2-({[(3'-Fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]amino}butanoic acid
168	N-[(3'-Fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-isoleucine
169	3-Cyclopropyl-N-[(3'-fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-alanine
170	N-[(4'-{[6-(Trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-valine

Example No.	IUPAC Name
171	N-[(4'-{[6-(Trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-leucine
172	N-[(4'-{[6-(Trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-norvaline
173	3-Methyl-N-[(4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-valine
174	(2S)-2-{[(4'-{[6-(Trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]amino}butanoic acid
175	N-[(4'-{[6-(Trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-isoleucine
176	3-Cyclopropyl-N-[(4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-alanine
177	N-({3'-Fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine
178	N-({3'-Fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine
179	N-({3'-Fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-norvaline
180	(2S)-2-[({3'-Fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid
181	N-({3'-Fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-methyl-L-valine
182	N-({3'-Fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-isoleucine
183	3-Cyclopropyl-N-({3'-fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine
184	N-[(4'-{[6-(Trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-leucine trifluoroacetate
185	N-[(4'-{[6-(Trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-norvaline trifluoroacetate
186	3-Methyl-N-[(4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-valine trifluoroacetate
187	(2S)-2-{[(4'-{[6-(Trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]amino}butanoic acid trifluoroacetate
188	N-[(4'-{[6-(Trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-isoleucine trifluoroacetate
189	3-Cyclopropyl-N-[(4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-alanine trifluoroacetate
190	N-[(3'-Fluoro-4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-leucine trifluoroacetate
191	N-[(3'-Fluoro-4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-norvaline trifluoroacetate
192	N-[(3'-Fluoro-4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-3-methyl-L-valine trifluoroacetate
193	(2S)-2-{[(3'-Fluoro-4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]amino}butanoic acid trifluoroacetate
194	N-[(3'-Fluoro-4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-isoleucine trifluoroacetate

Example No.	IUPAC Name
195	N-({4'-[(7-Chloro[1,3]thiazolo[5,4-c]pyridin-2-yl)amino]-3'-fluorobiphenyl-4-yl}carbonyl)-L-valine trifluoroacetate

Methods of Use

[237] As used herein, various terms are defined below.

[238] When introducing elements of the present invention or the preferred embodiment(s) thereof, the articles "a," "an," "the," and "said" are intended to mean that there are one or more of the elements. The terms "comprising," "including," and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

[239] The term "subject" as used herein includes mammals (e.g., humans and animals).

[240] The term "treatment" includes any process, action, application, therapy, or the like, wherein a subject, including a human being, is provided medical aid with the object of improving the subject's condition, directly or indirectly, or slowing the progression of a condition or disorder in the subject.

[241] The term "combination therapy" or "co-therapy" means the administration of two or more therapeutic agents to treat a disease, condition, and/or disorder. Such administration encompasses co-administration of two or more therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each inhibitor agent. In addition, such administration encompasses use of each type of therapeutic agent in a sequential manner.

[242] The phrase "therapeutically effective" means the amount of each agent administered that will achieve the goal of improvement in a disease, condition, and/or disorder severity, while avoiding or minimizing adverse side effects associated with the given therapeutic treatment.

[243] The term "pharmaceutically acceptable" means that the subject item is appropriate for use in a pharmaceutical product.

[244] The compounds of Formula (I) of this invention are expected to be valuable as therapeutic agents. Accordingly, an embodiment of this invention includes a method of treating the various conditions in a patient (including mammals) which comprises administering to said patient a composition containing an amount of the compound of Formula (I) that is effective in treating the target condition.

[245] This invention relates to compounds that may be useful for the regulation of food intake (e.g., stimulation and suppression). For example, an object of this invention is to provide methods for

treating obesity and inducing weight loss in an individual by administration of a compound of the invention. The method of the invention comprises administering to an individual a therapeutically effective amount of at least one compound of the invention, or a prodrug thereof, which is sufficient to induce weight loss. The invention further comprises a method of preventing weight gain in an individual by administering an amount of at least one compound of the invention, or a prodrug thereof, which is sufficient to prevent weight gain.

[246] The present invention also relates to the use of the compounds of this invention for the treatment of obesity-related diseases including associated dyslipidemia and other obesity- and overweight-related complications such as, for example, cholesterol gallstones, gallbladder disease, gout, cancer (e.g., colon, rectum, prostate, breast, ovary, endometrium, cervix, gallbladder, and bile duct), menstrual abnormalities, infertility, polycystic ovaries, osteoarthritis, and sleep apnea, as well as for a number of other pharmaceutical uses associated therewith, such as the regulation of appetite and food intake, dyslipidemia, hypertriglyceridemia, Syndrome X, type 2 diabetes (non-insulin-dependent diabetes), atherosclerotic diseases such as heart failure, hyperlipidemia, hypercholesteremia, low HDL levels, hypertension, cardiovascular disease (including atherosclerosis, coronary heart disease, coronary artery disease, and hypertension), cerebrovascular disease such as stroke, and peripheral vessel disease. The compounds of this invention may also be useful for treating physiological disorders related to, for example, regulation of insulin sensitivity, inflammatory response, plasma triglycerides, HDL, LDL and cholesterol levels and the like.

[247] Compounds of Formula (I) may be administered alone or in combination with one or more additional therapeutic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of Formula (I) and one or more additional therapeutic agents, as well as administration of the compound of Formula (I) and each additional therapeutic agents in its own separate pharmaceutical dosage formulation. For example, a compound of Formula (I) and a therapeutic agent may be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent may be administered in separate oral dosage formulations.

[248] Where separate dosage formulations are used, a compound of Formula (I) and one or more additional therapeutic agents may be administered at essentially the same time (e.g., concurrently) or at separately staggered times (e.g., sequentially).

[249] For example, a compound of Formula (I) may be used in combination with other therapies and drugs useful for the treatment of obesity. For example, anti-obesity drugs include β-3 adrenergic receptor agonists such as CL 316,243; cannabinoid (e.g., CB-1) antagonists such as Rimonabant;

neuropeptide-Y receptor antagonists; neuropeptide Y5 inhibitors; apo-B/MTP inhibitors; 11β-hydroxy steroid dehydrogenase-1 inhibitors; peptide YY_{3-36} or analogs thereof; MCR4 agonists; CCK-A agonists; monoamine reuptake inhibitors; sympathomimetic agents; dopamine agonists; melanocyte-stimulating hormone receptor analogs; melanin concentrating hormone antagonists; leptin; leptin analogs; leptin receptor agonists; galanin antagonists; lipase inhibitors; bombesin agonists; thyromimetic agents; dehydroepiandrosterone or analogs thereof; glucocorticoid receptor antagonists; orexin receptor antagonists; ciliary neurotrophic factor; ghrelin receptor antagonists; histamine-3 receptor antagonists; neuromedin U receptor agonists; appetite suppressants, such as, for example, sibutramine (Meridia); and lipase inhibitors, such as, for example, orlistat (Xenical). The compounds of the present invention may also be administered in combination with a drug compound that modulates digestion and/or metabolism such as drugs that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

[250] In addition, a compound of Formula (I) may be administered in combination with one or more of the following agents for the treatment of diabetes or diabetes-related disorders including PPAR ligands (agonists, antagonists), insulin secretagogues, for example, sulfonylurea drugs and non-sulfonylurea secretagogues, α-glucosidase inhibitors, insulin sensitizers, hepatic glucose output lowering compounds, and insulin and insulin derivatives. Such therapies may be administered prior to, concurrently with, or following administration of the compounds of the invention. Insulin and insulin derivatives include both long and short acting forms and formulations of insulin. PPAR ligands may include agonists and/or antagonists of any of the PPAR receptors or combinations thereof. For example, PPAR ligands may include ligands of PPAR-α, PPAR-γ, PPAR-δ or any combination of two or three of the receptors of PPAR. PPAR ligands include, for example, rosiglitazone, troglitazone, and pioglitazone. Sulfonylurea drugs include, for example, glyburide, glimepiride, chlorpropamide, tolbutamide, and glipizide. α-glucosidase inhibitors that may be useful in treating diabetes when administered with a compound of the invention include acarbose, miglitol, and voglibose. Insulin sensitizers that may be useful in treating diabetes include PPAR-γ agonists such as the glitazones (e.g., troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like) and other thiazolidinedione and non-thiazolidinedione compounds; biguanides such as metformin and phenformin; protein tyrosine phosphatase-1B (PTP-1B) inhibitors; dipeptidyl peptidase IV (DPP-IV) inhibitors, and 11beta-HSD inhibitors. Hepatic glucose output lowering compounds that may be useful in treating diabetes when administered with a compound of the invention include glucagon antagonists and metformin, such as Glucophage and Glucophage XR. Insulin secretagogues that may be useful in treating diabetes when administered with a compound of the invention include sulfonylurea and non-sulfonylurea drugs: GLP-1, GIP, PACAP, secretin, and derivatives thereof; nateglinide, meglitinide, repaglinide, glibenclamide, glimepiride, chlorpropamide,

glipizide. GLP-1 includes derivatives of GLP-1 with longer half-lives than native GLP-1, such as, for example, fatty-acid derivatized GLP-1 and exendin.

[251] Compounds of the invention may also be used in methods of the invention in combination with drugs commonly used to treat lipid disorders in patients. Such drugs include, but are not limited to, HMG-CoA reductase inhibitors, nicotinic acid, fatty acid lowering compounds (e.g., acipimox); lipid lowering drugs (e.g., stanol esters, sterol glycosides such as tiqueside, and azetidinones such as ezetimibe), ACAT inhibitors (such as avasimibe), bile acid sequestrants, bile acid reuptake inhibitors, microsomal triglyceride transport inhibitors, and fibric acid derivatives. HMG-CoA reductase inhibitors include, for example, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, cerivastatin, and ZD-4522. Fibric acid derivatives include, for example, clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate, etofibrate, and gemfibrozil. Sequestrants include, for example, cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran.

[252] Compounds of the invention may also be used in combination with anti-hypertensive drugs, such as, for example, β-blockers and ACE inhibitors. Examples of additional anti-hypertensive agents for use in combination with the compounds of the present invention include calcium channel blockers (L-type and T-type; e.g., diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan, neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

[253] The compound of Formula (I) may also be utilized, in free base form or in compositions, as well as in research and diagnostics or as analytical reference standards, and the like, which are well known in the art. Therefore, the present invention includes compositions which are comprised of an inert carrier and an effective amount of a compound of Formula (I), or a salt, or ester thereof. An inert carrier is any material which does not interact with the compound to be carried and which lends support, means of conveyance, bulk, traceable material, and the like to the compound to be carried. An effective amount of the compound is that amount which produces a result or exerts an influence on the particular procedure being performed.

[254] It is anticipated that prodrug forms of the compounds of this invention will prove useful in certain circumstances, and such compounds are also intended to fall within the scope of the invention.

Prodrug forms may have advantages over the parent compounds exemplified herein, in that they are better absorbed, better distributed, more readily penetrate the central nervous system, are more slowly metabolized or cleared, etc. Prodrug forms may also have formulation advantages in terms of crystallinity or water solubility. For example, compounds of the invention having one or more hydroxyl groups may be converted to esters or carbonates bearing one or more carboxyl, hydroxyl or amino groups, which are hydrolyzed at physiological pH values or are cleaved by endogenous esterases or lipases *in vivo* (*see, e.g.*, U.S. Patent Nos. 4,942,184; 4,960,790; 5,817,840; and 5,824,701, all of which are incorporated herein by reference in their entirety, and references therein).

Pharmaceutical Compositions

[255] Based on the above tests, or other well known assays used to determine the efficacy for treatment of conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

[256] The total amount of the active ingredient to be administered may generally range, for example, from about 0.001 mg/kg to about 200 mg/kg. A unit dosage may contain from, for example, about 0.05 mg to about 1500 mg of active ingredient, and may be administered one or more times per day. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous, and parenteral injections, and use of infusion techniques may be from, for example, about 0.01 to about 200 mg/kg. The daily rectal dosage regimen may be from, for example, 0.01 to 200 mg/kg of total body weight. The transdermal concentration may be that required to maintain a daily dose of from, for example, 0.01 to 200 mg/kg.

[257] Of course, the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age of the patient, the diet of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt thereof may be ascertained by those skilled in the art using conventional treatment tests.

[258] The compounds of this invention may be utilized to achieve the desired pharmacological effect by administration to a subject in need thereof in an appropriately formulated pharmaceutical

composition. A subject, for example, may be a mammal, including a human, in need of treatment for a particular condition or disease. Therefore, the present invention includes pharmaceutical compositions which are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound identified by the methods described herein, or a pharmaceutically acceptable salt or ester thereof. A pharmaceutically acceptable carrier is any carrier which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of a compound is that amount which produces a result or exerts an influence on the particular condition being treated. The compounds identified by the methods described herein may be administered with a pharmaceutically-acceptable carrier using any effective conventional dosage unit forms, including, for example, immediate and timed release preparations, orally, parenterally, topically, or the like.

[259] For oral administration, the compounds may be formulated into solid or liquid preparations such as, for example, capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms may be a capsule which can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

[260] In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with binders such as acacia, cornstarch, or gelatin; disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum; lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example, talc, stearic acid, or magnesium, calcium or zinc stearate; dyes; coloring agents; and flavoring agents intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

[261] Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, those sweetening,

flavoring and coloring agents described above, may also be present.

[262] The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[263] Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol, or sucrose. Such formulations may also contain a demulcent, and preservative, flavoring and coloring agents.

[264] The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intramuscularly, or interperitoneally, as injectable dosages of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which may be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions; an alcohol; glycols; glycerol ketals; ethers; an oil; a fatty acid; a fatty acid ester or glyceride; or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant; suspending agent; or emulsifying agent and other pharmaceutical adjuvants.

[265] The parenteral compositions of this invention may typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulation ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

[266] The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents, dispersing or wetting agents which may be a naturally occurring phosphatide, a condensation product of an alkylene oxide with a fatty acid, a condensation product of ethylene oxide with a long chain aliphatic alcohol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride.

[267] The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be

employed are, for example, water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid may be used in the preparation of injectables.

[268] A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such material are, for example, cocoa butter and polyethylene glycol.

[269] Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (*see*, e.g., U.S. Patent No. 5,023,252, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[270] It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. For example, direct techniques for administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in U.S. Patent No. 5,011,472, incorporated herein by reference.

[271] Another formulation employs the use of biodegradable microspheres that allow controlled, sustained release. Such formulations can be comprised of synthetic polymers or copolymers. Such formulations allow for injection, inhalation, nasal or oral administration. The construction and use of biodegradable microspheres for the delivery of pharmaceutical agents is well known in the art (e.g., US Patent No. 6, 706,289, incorporated herein by reference).

[272] The compositions of the invention may also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Any of the compositions of this invention may be preserved by the addition of an antioxidant such as ascorbic acid or by other suitable preservatives. Conventional procedures for preparing such

compositions in appropriate dosage forms can be utilized.

[273] The compounds identified by the methods described herein may be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. For example, the compounds of this invention can be combined with known anti-obesity, or with known antidiabetic or other indication agents, and the like, as well as with admixtures and combinations thereof.

[274] The compounds identified by the methods described herein may also be utilized, in free base form or in compositions, in research and diagnostics, or as analytical reference standards, and the like. Therefore, the present invention includes compositions which are comprised of an inert carrier and an effective amount of a compound identified by the methods described herein, or a salt or ester thereof. An inert carrier is any material which does not interact with the compound to be carried and which lends support, means of conveyance, bulk, traceable material, and the like to the compound to be carried. An effective amount of compound is that amount which produces a result or exerts an influence on the particular procedure being performed.

[275] Formulations suitable for subcutaneous, intravenous, intramuscular, and the like; suitable pharmaceutical carriers; and techniques for formulation and administration may be prepared by any of the methods well known in the art (*see, e.g.*, Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 20th edition, 2000)

[276] The structures, materials, compositions, and methods described herein are intended to be representative examples of the invention, and it will be understood that the scope of the invention is not limited by the scope of the examples. Those skilled in the art will recognize that the invention may be practiced with variations on the disclosed structures, materials, compositions and methods, and such variations are regarded as within the ambit of the invention.

BIOLOGICAL ACTIVITY OF THE COMPOUNDS

[277] In order that this invention may be better understood, the following examples are set forth. These examples are for the purpose of illustration only, and are not to be construed as limiting the scope of the invention in any manner. All publications mentioned herein are incorporated by reference in their entirety.

[278] Demonstration of the activity of the compounds of the present invention may be accomplished through *in vitro*, *ex vivo*, and *in vivo* assays that are well known in the art. For example, to demonstrate the efficacy of a pharmaceutical agent for the treatment of obesity and related disorders, the following assays may be used.

Evaluation of Compound Effect on the Inhibition of DGAT-1 Enzyme Activity

[279] The human DGAT-1 gene (*see, e.g.*, U.S. Patent No. 6,100,077) was isolated from a human cDNA library by PCR. Recombinant AcNPV baculovirus was constructed in which the gene for occlusion body forming protein polyhedrin was replaced with the DGAT-1 gene. The DGAT-1 gene sequence was inserted into the AcNPV genome 3' to the polyhedrin promoter sequence placing DGAT-1 under the transcriptional control of the polyhedrin promoter. Spodoptera frugiperda-derived Sf9 insect cells were infected with DGAT-1-containing recombinant baculovirus at the multiplicity of infection of 5 and harvested 48 h post-infection. DGAT-1-expressing insect cells were homogenized in 10 mM Tris, 250 mM sucrose, pH 7.5 at the concentration of 100 mg of wet cell biomass per mL. The homogenate was centrifuged at 25,000 g for 30 min. The 25,000 g pellet was discarded and the supernatant was centrifuged at 100,000 g for 1 h. The 100,000 g supernatant was discarded and the 100,000 g DGAT-1-containing membrane pellet was re-suspended in 10 mM Tris, 50% (v/v) glycerol pH 7.5.

[280] DGAT-1 enzyme activity was determined by a phase partitioning protocol. Specifically, DGAT-1 containing membranes were incubated in 20 mM didecanoyl glycerol, 5 mM ^{14}C-decanoyl-CoA, 2 mM $MgCl_2$, 0.01 % BSA, 50 mM HEPES, pH 7.5 buffer in the presence of varying concentrations of inhibitors. Assays were performed in 100 µL volumes in 96-well microtiter plates with 0.5 µg of total membrane protein per well. The assay was initiated by substrate and mixed gently for 1 h at ambient temperature. Activity was quenched by the addition of 25 µL of 0.1 % phosphoric acid solution. Selective extraction of the hydrophobic tridecanolyglycerol product was accomplished by the addition of 150 µL phase partitioning scintillation fluid Microscint® (Packard, Inc.) and vigorous mixing for 30 min. Quantification of the product was accomplished by a MicroBeta® scintillation counter (Wallac, Inc.) after settling for approximately 16 h at ambient temperatures.

Evaluation of Compound Effect on the Inhibition of Cellular Triglyceride Deposition

[281] The cell-based assay for DGAT-1 was conducted with human colorectal adenocarcinoma cells HT-29 (HTB-38, ATCC). HT-29 cells were grown in 75 cm^2 plate until ~90% confluent in DMEM media with 10% FBS, PSF, glutamine, and 10 mM acetate. Cells were then re-plated in 24-well plates to give 1:1.2 dilution and grown approximately 16 h. Triacylglyceride formation was stimulated by the addition of lauric acid to 0.01% final concentration in the presence of varying concentrations of inhibitors. After 6 h, cells were released from the plate by trypsin, collected by centrifugation, re-suspended in water, transferred to glass HPLC, frozen at –70°C, and lyophilized. Freeze dried cell pellets were re-suspended in 150 µL HPLC grade tetrohydrofuran and sealed in the vials. Vials were sonnicated for 30 min with heating in a sonicating water bath (Fisher, Inc.). Cellular triacylglycerides were quantified by HPLC (HP1100, Agilent, Inc.) utilizing evaporative light-scattering detection (PL-ELS 1000, Polymer Labs, Inc.). Chromatographic separation was accompliahed by 30 to 100% B buffer in 4 min followed by 3 min at 100% B buffer using a PLRP S 100 column (5 micron, 150 x 4.6 mm, Polymer Labs, Inc.) at 50°C (A: 50% acetonitrile, 2.5% methanol, B: 100% tetrohydrofuran). Sample injections were 20 µL and the detector was set at 0.4 SLM, 40°C nebulizer, and 80°C evaporator. Non-polar fatty acids and glycerol lipids were identified and quantified by using commercially available standards.

Evaluation of Compound Efficacy on the Reduction of Body Weight in Diet-Induced Obese Mice.

[282] The purpose of this protocol is to determine the effect of chronic administration of a compound on the body weight of mice made obese by exposure to a 45% kcal/g high fat diet for more than 10 weeks. The body weight of mice selected for these studies was higher than three standard deviations from the weight of a control group of mice fed standard low fat (5-6% fat) mouse chow. Diet-induced obese (DIO) animals have been used frequently in the determination of compound efficacy in the reduction of body weight (*see, e.g.*, Brown, et al., Brit. J. Pharmacol. 132:1898-1904, 2001; Guerre-Millo, et al., J. Biol. Chem. 275(22):16638-42, 2000; Han, et al., Intl. J. Obesity and Related Metabolic Disorders 23(2):174-79, 1999; Surwit, et al., Endocrinol. 141(10):3630-37, 2000).

[283] This animal model has been successfully used in the identification and characterization of the efficacy profile of compounds that are or have been used in the management of body weight in obese humans (*see, e.g.*, Brown, et al., 2001; Guerre-Millo, et al., 2000; Han, et al., 1999).

[284] A typical study included 60-80 male C57bl/J6 mice (n = 10/treatment group) with an average body weight of approximately 45 g. Mice are kept in standard animal rooms under controlled temperature and humidity and a 12 hour/12 hour light/dark cycle. Water and food are continuously available. Mice were individually housed. Animals are sham dosed with study vehicle for at least

four days before the recording of two-day baseline measurements of body weight and 24-hour food and water consumption. Mice are assigned to one of 6-8 treatment groups based upon their body weight on baseline. The groups are set up so that the mean and standard error of the mean of body weight were similar.

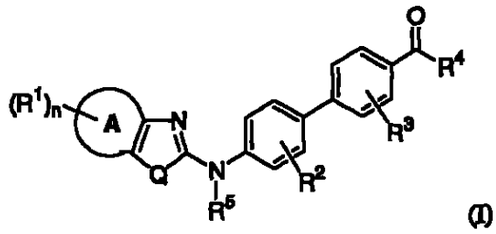
[285] Animals are orally gavaged (5 mL/kg) daily before the dark phase of the light/dark cycle for a pre-determined number of days (typically 8-14 days) with their assigned dose/compound. Body weight, and food and water consumption are measured. Data is analyzed using appropriate statistics following the research design. On the final day, animals are euthanized using CO_2 inhalation.

[286] Compounds are typically dosed at 1 to 30 mg/kg p.o. q.d., and compounds are considered to be active if a statistically significant reduction in weight was observed for the treated animals, relative to vehicle-treated control animals.

[287] The structures, materials, compositions, and methods described herein are intended to be representative examples of the invention, and it will be understood that the scope of the invention is not limited by the scope of the examples. Those skilled in the art will recognize that the invention may be practiced with variations on the disclosed structures, materials, compositions and methods, and such variations are regarded as within the ambit of the invention.

Claims:

1. A compound of Formula (I)



(I)

wherein

Q is O, NR^{11}, or S;

A is a fused ring selected from

an aromatic 6-membered ring containing 0 or 1 N atoms;

R^1 is independently selected from

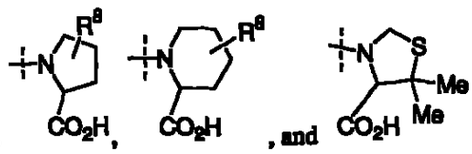
halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, cyano, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, aminocarbonyl, (C_1-C_6)alkylaminocarbonyl, bis[(C_1-C_6)alkyl]aminocarbonyl, aminosulfonyl, (C_1-C_6)alkylaminosulfonyl, bis[(C_1-C_6)alkyl]aminosulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl,

and

when two of said R^1 substituents are (C_1-C_6)alkyl and are attached to adjacent carbon atoms of the Ring A, they may be joined together to form a 5-7-membered carbocyclic ring;

n is 0, 1, or 2;

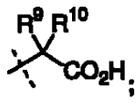
R^2 and R^3 are independently selected from hydrogen, halo, hydroxy, (C_1-C_6)alkyl, trifluoromethyl, (C_1-C_6)alkoxy, and trifluoromethoxy;

R^4 is selected from 

wherein

R^6 is H or CH_3;

and

R^7 is  ;

wherein

R^9 is selected from

$(C_1$-$C_6)$alkyl optionally substituted with one or two groups selected from vinyl, CF_3, OH, methoxy, SCH_3, NH_2, $-CO_2H$, and $-CONH_2$,

$(CH_2)_m$phenyl wherein m is 0 to 3, and

where the phenyl ring is optionally substituted with one or two groups selected from halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, OH, nitro, and cyano,

piperidinyl optionally substituted on C with halo and optionally substituted on C or N with $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, nitro, or cyano,

tetrahydropyran-4-yl;

R^{10} is H or methyl;

or

R^9 and R^{10} may form, together with the carbon to which they are attached, a 3- to 6-membered carbocyclic ring,

R^8 is hydrogen, $(C_1$-$C_4)$alkyl, hydroxy, or methoxy;

R^5 is selected from H, $(C_1$-$C_6)$alkyl, and hydroxy-$(C_2$-$C_6)$alkyl;

R^{11} is selected from H, $(C_1$-$C_6)$alkyl, and hydroxy-$(C_2$-$C_6)$alkyl;

and the pharmaceutically acceptable salts and esters thereof.

2. The compound of claim 1, wherein

Q is O, NR^{11}, or S;



is a fused ring selected from

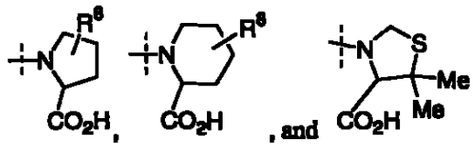
an aromatic 6-membered ring containing 0 or 1 N atoms;

R^1 is independently selected from

halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, cyano, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, aminocarbonyl, (C_1-C_6)alkylaminocarbonyl, bis[(C_1-C_6)alkyl]aminocarbonyl, aminosulfonyl, (C_1-C_6)alkylaminosulfonyl, bis[(C_1-C_6)alkyl]aminosulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl;

n is 0, 1, or 2;

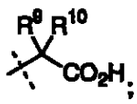
R^2 and R^3 are independently selected from hydrogen, halo, hydroxy, (C_1-C_6)alkyl, trifluoromethyl, (C_1-C_6)alkoxy, and trifluoromethoxy;

R^4 is selected from 

wherein

R^6 is H or CH_3;

and

R^7 is  ;

wherein

R^9 is selected from

(C_1-C_6)alkyl optionally substituted with one or two groups selected from vinyl, CF_3, OH, methoxy, SCH_3, NH_2, $-CO_2H$, and $-CONH_2$,

$(CH_2)_m$phenyl wherein m is 0 to 3, and

where the phenyl ring is optionally substituted with one or two groups selected from halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, OH, nitro, and cyano,

piperidinyl optionally substituted on C with halo and optionally substituted on C or N with (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, or cyano,

tetrahydropyran-4-yl;

R^{10} is H or methyl;

or

R^9 and R^{10} may form, together with the carbon to which they are attached, a 3- to 6-membered carbocyclic ring,

R^8 is hydrogen, (C_1-C_4)alkyl, hydroxy, or methoxy;

R^5 is selected from H, (C_1-C_6)alkyl, and hydroxy-(C_2-C_6)alkyl; and

R^{11} is selected from H, (C_1-C_6)alkyl, and hydroxy-(C_2-C_6)alkyl.

3. The compound of claim 1, wherein

Q is O, NR^{11}, or S;



is a fused ring selected from

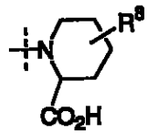
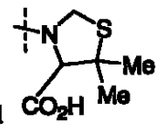
an aromatic 6-membered ring containing 0 or 1 N atoms;

R^1 is independently selected from

halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, cyano, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, aminocarbonyl, (C_1-C_6)alkylaminocarbonyl, bis[(C_1-C_6)alkyl]aminocarbonyl, aminosulfonyl, (C_1-C_6)alkylaminosulfonyl, bis[(C_1-C_6)alkyl]aminosulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl;

n is 0, 1, or 2;

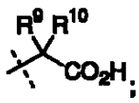
R^2 and R^3 are independently selected from hydrogen, halo, hydroxy, (C_1-C_6)alkyl, trifluoromethyl, (C_1-C_6)alkoxy, and trifluoromethoxy;

R^4 is selected from $-NR^6R^7$,  , and 

wherein

R^6 is H or CH_3;

and

R^7 is  ;

wherein

R^9 is selected from

(C_1-C_6)alkyl optionally substituted with one or two groups selected from vinyl, CF_3, OH, methoxy, SCH_3, NH_2, $-CO_2H$, and $-CONH_2$,

$(CH_2)_m$phenyl wherein m is 0 to 3, and

where the phenyl ring is optionally substituted with one or two groups selected from halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, OH, nitro, and cyano,

piperidinyl optionally substituted on C with halo and optionally substituted on C or N with (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, or cyano,

tetrahydropyran-4-yl;

R^{10} is H or methyl;

or

R^9 and R^{10} may form, together with the carbon to which they are attached, a 3- to 6-membered carbocyclic ring,

R^8 is hydrogen, (C_1-C_4)alkyl, hydroxy, or methoxy;

R^5 is selected from H, (C_1-C_6)alkyl, and hydroxy-(C_2-C_6)alkyl; and

R^{11} is selected from H, (C_1-C_6)alkyl, and hydroxy-(C_2-C_6)alkyl.

4. The compound of claim 1, wherein

Q is S;



is a fused ring selected from

an aromatic 6-membered ring containing 0 or 1 N atoms;

R^1 is independently selected from

halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, cyano, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, aminocarbonyl, (C_1-C_6)alkylaminocarbonyl, bis[(C_1-C_6)alkyl]aminocarbonyl, aminosulfonyl, (C_1-C_6)alkylaminosulfonyl, bis[(C_1-C_6)alkyl]aminosulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl;

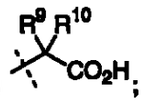
n is 0, 1, or 2;

R^2 and R^3 are independently selected from hydrogen, halo, hydroxy, (C_1-C_6)alkyl, trifluoromethyl, (C_1-C_6)alkoxy, and trifluoromethoxy;

R^4 is  , wherein

R^6 is H or CH_3;

and

R^7 is  ;

wherein

R^9 is selected from

(C_1-C_6)alkyl optionally substituted with one or two groups selected from vinyl, CF_3, OH, methoxy, SCH_3, NH_2, $-CO_2H$, and $-CONH_2$,

$(CH_2)_m$phenyl wherein m is 0 to 3, and

where the phenyl ring is optionally substituted with one or two groups selected from halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, OH, nitro, and cyano,

piperidinyl optionally substituted on C with halo and optionally substituted on C or N with (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, or cyano,

tetrahydropyran-4-yl;

R^{10} is H or methyl;

or

R^9 and R^{10} may form, together with the carbon to which they are attached, a 3- to 6-membered carbocyclic ring,

R^8 is hydrogen, (C_1-C_4)alkyl, hydroxy, or methoxy;

R^5 is selected from H, (C_1-C_6)alkyl, and hydroxy-(C_2-C_6)alkyl; and

R^{11} is selected from H, (C_1-C_6)alkyl, and hydroxy-(C_2-C_6)alkyl.

5. The compound of claim 1 selected from

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine,
N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine,
N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine,
N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine,
N-({3-chloro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine,
N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine,
N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine,
N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine,
N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine,
N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-leucine,
N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-leucine,
N-({3-chloro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-leucine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-leucine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-D-leucine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-D-leucine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-isoleucine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-isoleucine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-isoleucine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-phenylalanine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-phenylalanine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-phenylalanine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-phenylalanine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-phenylalanine,

N-({3-chloro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-phenylalanine,

1-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-proline,

1-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-proline,

1-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-proline,

1-({3-chloro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-proline,

1-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-proline,

1-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-proline,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-2-methylalanine,

N-({3-chloro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-2-methylalanine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-2-methylalanine,

1-[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino] cyclopropanecarboxylic acid,

1-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino] cyclopropanecarboxylic acid,

1-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl} carbonyl)amino]cyclopropanecarboxylic acid,

1-[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino] cyclopentanecarboxylic acid,

1-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino] cyclopentanecarboxylic acid,

1-[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino] cyclohexanecarboxylic acid,

(2S)-2-[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid,

(2S)-2-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino] butanoic acid,

(2S)-2-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)amino]butanoic acid,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-norvaline,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-norvaline,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-norvaline,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-methyl-L-valine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-methyl-L-valine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-3-methyl-L-valine,

4-chloro-N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl) phenylalanine,

(2S)-cyclohexyl[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino] acetic acid,

[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino](tetrahydro-2H-pyran-4-yl)acetic acid,

[1-(tert-butoxycarbonyl)piperidin-4-yl][({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]acetic acid,

[1-(tert-butoxycarbonyl)piperidin-3-yl][({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]acetic acid,

[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino](piperidin-3-yl)acetic acid,

1-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)piperidine-2-carboxylic acid,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine,

N-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine,

N-{[4'-(1,3-benzothiazol-2-ylamino)-3-methylbiphenyl-4-yl]carbonyl}-L-valine,

N-({4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine,

N-({4'-[(7-fluoro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine,

N-({4'-[(7-chloro-1,3-benzothiazol-2-yl)amino]-3-methylbiphenyl-4-yl}carbonyl)-L-valine,

N-{[4'-(1,3-benzothiazol-2-ylamino)-3-methoxybiphenyl-4-yl]carbonyl}-L-valine,

N-{[4'-(1,3-benzothiazol-2-ylamino)biphenyl-4-yl]carbonyl}-L-valine,

N-{[4'-(1,3-benzothiazol-2-ylamino)biphenyl-4-yl]carbonyl}-D-valine,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine,

N-({4'-[(7-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine,

N-({4'-[(7-chloro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine,

N-({4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-valine,

N-{[4'-(1,3-benzothiazol-2-ylamino)-3-chlorobiphenyl-4-yl]carbonyl}-L-valine,

N-({3-chloro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine,

N-({3-chloro-4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine,

N-({3-chloro-4'-[(7-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine,

N-({3-chloro-4'-[(7-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine,

N-{[4'-(1,3-benzothiazol-2-ylamino)-3-methoxybiphenyl-4-yl]carbonyl}-L-leucine,

N-({3-methoxy-4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-leucine,

N-({4'-[(4-chloro-6-fluoro-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-leucine,

N-({3-methoxy-4'-[(6-nitro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine,

N-[(3-methoxy-4'-{[6-(methylsulfonyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-leucine,

N-({4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]-3-methoxybiphenyl-4-yl}carbonyl)-L-leucine,

N-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine,

N-{[4'-(1,3-benzothiazol-2-ylamino)biphenyl-4-yl]carbonyl}-2-methylalanine,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-2-methylalanine,

N-{[4'-(1,3-benzothiazol-2-ylamino)biphenyl-4-yl]carbonyl}-N-methyl-L-alanine,

N-{[4'-(1,3-benzothiazol-2-ylamino)biphenyl-4-yl]carbonyl}-N-methyl-L-valine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-allothreonine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-allothreonine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-threonine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-threonine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-serine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-O-methyl-L-serine,

3-cyclopropyl-N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-O-methyl-L-serine,

3-cyclopropyl-N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-N-methyl-L-valine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-N-methyl-L-valine,

N-({3-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine,

N-({3-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine,

N-({3-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-methyl-L-valine,

N-({3-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-isoleucine,

N-({3-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-norvaline,

(2S)-2-[({3-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid,

3-cyclopropyl-N-({3-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine,

N-({3,3'-difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine,

N-({3,3'-difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine,

N-({3,3'-difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-methyl-L-valine,

N-({3,3'-difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-norvaline,

(2S)-2-[({3,3'-difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid,

3-cyclopropyl-N-({3,3'-difluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine,

N-[(3'-fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-valine,

N-[(3'-fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-leucine,

N-[(3'-fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-norvaline,

N-[(3'-fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-isoleucine,

N-[(3'-fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-3-methyl-L-valine,

3-cyclopropyl-N-[(3'-fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-alanine,

(2S)-2-{[(3'-fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]amino}butanoic acid,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3'-fluorobiphenyl-4-yl}carbonyl)-L-leucine,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-norvaline,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-isoleucine,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-methyl-L-valine,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3'-fluorobiphenyl-4-yl}carbonyl)-L-valine,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3'-fluorobiphenyl-4-yl}carbonyl)-L-norvaline,

(2S)-2-[({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3'-fluorobiphenyl-4-yl}carbonyl)amino]butanoic acid,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-cyclopropyl-L-alanine,

N-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3'-fluorobiphenyl-4-yl}carbonyl)-3-methyl-L-valine,

(2S)-2-[({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid,

N-{[4'-([1,3]thiazolo[5,4-b]pyridin-2-ylamino)biphenyl-4-yl]carbonyl}-L-valine,

N-{[4'-([1,3]thiazolo[4,5-c]pyridin-2-ylamino)biphenyl-4-yl]carbonyl}-L-valine,

N-{[4'-([1,3]thiazolo[4,5-b]pyridin-2-ylamino)biphenyl-4-yl]carbonyl}-L-valine,

N-[(3'-fluoro-4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-valine,

N-{[3'-fluoro-4'-([1,3]thiazolo[4,5-c]pyridin-2-ylamino)biphenyl-4-yl]carbonyl}-L-valine,

N-{[3'-fluoro-4'-([1,3]thiazolo[4,5-b]pyridin-2-ylamino)biphenyl-4-yl]carbonyl}-L-valine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-O-methyl-L-allothreonine,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-N-methyl-L-norvaline,

4,4,4-trifluoro-2-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino]butanoic acid,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-4-methylene-L-norvaline,

3-cyclobutyl-N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine,

(2S)-[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino](phenyl)acetic acid,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-O-methyl-L-allothreonine,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-N-methyl-L-norvaline,

1-[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)(methyl)amino] cyclopropanecarboxylic acid,

(4R)-3-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid,

4,4,4-trifluoro-2-[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl) amino]butanoic acid,

N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-4-methylene-L-norvaline,

3-cyclobutyl-N-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine,

(2*S*)-[({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)amino] (phenyl)acetic acid,

N-[(3'-fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-valine,

N-[(3'-fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-leucine,

N-[(3'-fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-norvaline,

N-[(3'-fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-3-methyl-L-valine,

(2*S*)-2-{[(3'-fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]amino}butanoic acid,

N-[(3'-fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-isoleucine,

3-cyclopropyl-N-[(3'-fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-alanine,

N-[(4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-valine,

N-[(4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-leucine,

N-[(4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-norvaline,

3-methyl-N-[(4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-valine,

(2S)-2-{[(4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl] amino}butanoic acid,

N-[(4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-isoleucine,

3-cyclopropyl-N-[(4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}biphenyl-4-yl)carbonyl]-L-alanine,

N-({3'-fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine,

N-({3'-fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-leucine,

N-({3'-fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-norvaline,

(2S)-2-[({3'-fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl) amino]butanoic acid,

N-({3'-fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-3-methyl-L-valine,

N-({3'-fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-isoleucine,

3-cyclopropyl-N-({3'-fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-alanine,

N-[(4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-leucine,

N-[(4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-norvaline,

3-methyl-N-[(4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-valine,

(2S)-2-{[(4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]amino}butanoic acid,

N-[(4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-isoleucine,

3-cyclopropyl-N-[(4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-alanine,

N-[(3'-fluoro-4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-leucine,

N-[(3'-fluoro-4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-norvaline,

N-[(3'-fluoro-4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-3-methyl-L-valine,

(2S)-2-{[(3'-fluoro-4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]amino}butanoic acid,

N-[(3'-fluoro-4'-{[6-(trifluoromethyl)[1,3]thiazolo[4,5-b]pyridin-2-yl]amino}biphenyl-4-yl)carbonyl]-L-isoleucine, and

N-({4'-[(7-chloro[1,3]thiazolo[5,4-c]pyridin-2-yl)amino]-3'-fluorobiphenyl-4-yl}carbonyl)-L-valine.

5. A pharmaceutical composition comprising an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier and one or more pharmaceutical agents.

7. The pharmaceutical composition of claim 6, wherein said pharmaceutical agent is selected from the group consisting of PPAR ligands, insulin secretagogues, sulfonylurea drugs, α-glucosidase inhibitors, insulin sensitizers, hepatic glucose output lowering compounds, insulin and insulin derivatives, biguanides, protein tyrosine phosphatase-1B, dipeptidyl peptidase IV, 11beta-HSD inhibitors, anti-obesity drugs, HMG-CoA reductase inhibitors, nicotinic acid, lipid lowering drugs, ACAT inhibitors, bile acid sequestrants, bile acid reuptake inhibitors, microsomal triglyceride transport inhibitors, fibric acid derivatives, β-blockers, ACE inhibitors, calcium channel blockers, diuretics, renin inhibitors, AT-1 receptor antagonists, ET receptor antagonists, neutral endopeptidase inhibitors, vasopepsidase inhibitors, and nitrates.

8. The pharmaceutical composition of claim 6, wherein said pharmaceutical agent is selected from β-3 adrenergic receptor agonists, cannabinoid antagonists, neuropeptide-Y receptor antagonists, neuropeptide Y5 inhibitors, apo-B/MTP inhibitors, 11β-hydroxy steroid dehydrogenase-1 inhibitors, peptide YY_{3-36} or analogs thereof, MCR4 agonists, CCK-A agonists, monoamine reuptake inhibitors, sympathomimetic agents, dopamine agonists, melanocyte-stimulating hormone receptor analogs, melanin concentrating hormone antagonists, leptin, leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors, bombesin agonists, thyromimetic agents, dehydroepiandrosterone or analogs

thereof, glucocorticoid receptor antagonists, orexin receptor antagonists, ciliary neurotrophic factor, ghrelin receptor antagonists, histamine-3 receptor antagonists, neuromedin U receptor agonists, appetite suppressants, and compound that modulates digestion and/or metabolism.

9. A method of regulating food intake comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 or a composition of claim 5.

10. A method of treating obesity or obesity-related disorders comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 or a composition of claim 5.

11. A method of treating diabetes or diabetes-related disorders comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 or a pharmaceutical composition of claim 5.

12. The method of claim 11, wherein said diabetes is selected from the group consisting of type 1 diabetes, type 2 diabetes, maturity-onset diabetes of the young, latent autoimmune diabetes adult, and gestational diabetes.

13. The method of claim 11, wherein said diabetes-related disorder is selected from the group consisting of hyperglycemia, hyperinsulinemia, impaired glucose tolerance, impaired fasting glucose, dyslipidemia, hypertriglyceridemia, and insulin resistance.

14. A method of regulating food intake comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 in combination with one or more pharmaceutical agents.

15. A method of treating obesity or obesity-related disorders comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 in combination with one or more pharmaceutical agents.

16. The method of claim 14 or 15, wherein said pharmaceutical agent is selected from β-3 adrenergic receptor agonists, cannabinoid antagonists, neuropeptide-Y receptor antagonists, neuropeptide Y5 inhibitors, apo-B/MTP inhibitors, 11β-hydroxy steroid dehydrogenase-1 inhibitors, peptide YY_{3-36} or analogs thereof, MCR4 agonists, CCK-A agonists, monoamine reuptake inhibitors, sympathomimetic agents, dopamine agonists, melanocyte-stimulating hormone receptor analogs, melanin concentrating hormone antagonists, leptin, leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors, bombesin agonists, thyromimetic agents, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor

antagonists, orexin receptor antagonists, ciliary neurotrophic factor, ghrelin receptor antagonists, histamine-3 receptor antagonists, neuromedin U receptor agonists, appetite suppressants, and compound that modulates digestion and/or metabolism.

17. A method of treating diabetes or diabetes-related disorders comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 in combination with one or more pharmaceutical agents.

18. The method of claim 17, wherein said pharmaceutical agent is selected from the group consisting of PPAR agonists, sulfonylurea drugs, non-sulfonylurea secretagogues, α-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, hepatic glucose output lowering compounds, insulin, and anti-obesity agents.

19. The method of claim 17, wherein said diabetes is selected from the group consisting of type 1 diabetes, type 2 diabetes, maturity-onset diabetes of the young, latent autoimmune diabetes adult, and gestational diabetes.

20. The method of claim 17, wherein said diabetes-related disorder is selected from the group consisting of hyperglycemia, hyperinsulinemia, impaired glucose tolerance, impaired fasting glucose, dyslipidemia, hypertriglyceridemia, and insulin resistance.

21. A method of treating obesity, obesity-related disorders, diabetes, or diabetes-related disorders comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 in combination with one or more agents selected from the group consisting of HMG-CoA reductase inhibitors, nicotinic acid, lipid lowering drugs, ACAT inhibitors, bile acid sequestrants, bile acid reuptake inhibitors, microsomal triglyceride transport inhibitors, fibric acid derivatives, β-blockers, ACE inhibitors, calcium channel blockers, diuretics, renin inhibitors, AT-1 receptor antagonists, ET receptor antagonists, neutral endopeptidase inhibitors, vasopepsidase inhibitors, and nitrates.

22. The method of claim 21, wherein said diabetes-related disorder is selected from the group consisting of hyperglycemia, hyperinsulinemia, impaired glucose tolerance, impaired fasting glucose, dyslipidemia, hypertriglyceridemia, and insulin resistance.

23. The method of any one of claims 14 to 22, wherein the compound of claim 1 and one or more pharmaceutical agents are administered as a single pharmaceutical dosage formulation.

24. A method of treating cardiovascular disease comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 or a pharmaceutical composition of claim 5.

25. The method of claim 24, wherein said cardiovascular disease is selected from atherosclerosis, coronary heart disease, coronary artery disease, and hypertension.

26. Compounds according to claim 1 for the treatment and/or prophylaxis of obesity, obesity-related disorders, diabetes, or diabetes-related disorders, or cardiovascular disease.

27. Medicament containing at least one compound according to claim 1 in combination with at least one pharmaceutically acceptable, pharmaceutically safe carrier or excipient.

28. Use of compounds according to claim 1 for manufacturing a medicament for the treatment and/or prophylaxis of diabetes, diabetes-related disorders, obesity, obesity-related disorders, or cardiovascular disease.

29. Medicaments according to claim 27 for the treatment and/or prophylaxis of obesity, obesity-related disorders, diabetes, diabetes-related disorders, or cardiovascular disease.

30. A method of treating diseases or disorders associated with DGAT-1 comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 or a composition of claim 5.

31. A method of treating diseases or disorders associated with DGAT-1 comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 in combination with one or more pharmaceutical agents.

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PREPARACIÓN Y USO DE DERIVADOS DE ÁCIDO BIFENIL-4-IL-CARBONILAMINO PARA EL TRATAMIENTO DE OBESIDAD

Esta solicitud reclama el beneficio de la Solicitud Provisional de E.U.A. Serie No. 60/618,975; presentada el 15 de octubre de 2004, el contenido de la cual se incorpora aquí por referencia en su totalidad.

CAMPO DE LA INVENCIÓN

Esta invención se refiere a ciertos compuestos de ácido bifenil-4-il carbonilamino, composiciones y métodos para tratar o prevenir obesidad y enfermedades relacionadas.

ANTECEDENTES DE LA INVENCIÓN

La obesidad, que es un exceso de grasa corporal en relación con la masa corporal magra, es una enfermedad crónica que prevalece altamente en la sociedad moderna. No solo está asociada a un estigma social, sino también al período de vida disminuido y numerosos problemas médicos, incluyendo desarrollo psicológico adverso, enfermedad de arterias coronarias, hipertensión, apoplejía, diabetes, hiperlipidemia y algunos cánceres (véase, v.gr., Nishina y otros, Metab. 43: 554-558, 1994; Grundy and Barnett, Dis.

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Mon. 36: 641-731, 1990; Risanen, y otros, British Medical Journal, 301: 835-837, 1990).

La obesidad sigue siendo un problema y se ha limitado el tratamiento, Por lo tanto, existe la necesidad de desarrollar fármacos y regímenes de tratamiento efectivos para aliviar la obesidad.

Una característica particular de obesidad es un incremento en masa de tejido adiposo blanco (TAB) lo cual se debe en gran parte a la acumulación de triacilglicerol. Este incremento de masa de TAB es un contribuyente clave para complicaciones asociados con obesidad. Las diacilglicerol O-aciltransferasas (DGAT, EC 2.3.1.2) son enzimas ligadas a membrana que catalizan el paso terminal de biosíntesis de triacilglicerol. Se han caracterizado dos enzimas que exhiben actividad de DGAT: DGAT-1 (diacilglicerol O-aciltransferasa tipo 1) (véase por ejemplo, Patente de E.U.A. No. 6,100,077; Cases, y otros, Proc. Nat. Acad. Sci. 95:13018-13023, 1998) y DGAT-2 (diacilglicerol O-aciltransferasa tipo 2) (Cases, y otros, J. Biol. Chem. 276: 38870-28876, 2001). Las DGAT-1 y DGAT-2 no exhiben identidad de secuencia de proteína significativa. De manera más importante, los ratones que anulan DGAT-1 no se vuelven obesos cuando se confrontan con una dieta alta en grasas en contraste con sus compañeros de jaula tipo silvestre (Smith, otros, Nature Genetics 25: 87-90, 2000). Los ratones con DGAT-1 nulo exhiben niveles de

glucosa en plasta posprandial y exhiben gasto de energía incrementado, pero tienen niveles normales de triglicéridos en suero (Smith, y otros, 2000), posiblemente debido a la actividad de DGAT-2 conservada. Dado que DGAT-1 se expresa en el intestino y tejido adiposo (Cases, y otros, 1998), por lo menos hay dos mecanismos posibles para explicar la resistencia de ratones con DGAT-1 nulo a la obesidad inducida por dieta. Primero, la supresión de la actividad de DGAT-1 en el intestino puede bloquear la reformación y exportación de triacilglicerol de células intestinales en la circulación vía partículas de quilomicras. Segundo, eliminando la actividad de DGAT-1 en el adiposito se puede disminuir el depósito de triacilglicerol en TAB. El fenotipo del ratón con DGAT-1 nulo, junto con los resultados de los estudios con inhibidores de DGAT-1 en ratones con obesidad inducida por dieta (OID), indica que el inhibidor de DGAT-1 tiene utilidad para el tratamiento de obesidad y complicaciones asociadas con obesidad.

SUMARIO DE LA INVENCIÓN

La presente invención se refiere a compuestos de ácido bifenil-4-il carbonilamino, composiciones y métodos para el tratamiento y prevención de obesidad y enfermedades relacionadas.

Consecuentemente, una modalidad de la presente invención es proveer compuestos como se describe en las Tablas y en los Ejemplos.

Otra modalidad de la invención es proveer un método para tratar o prevenir obesidad y enfermedades relacionadas en un sujeto que comprende administrar a un sujeto que necesita el mismo una cantidad efectiva de por lo menos un compuesto de la invención.

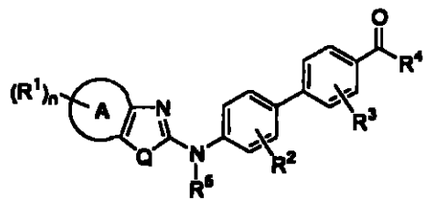
Una modalidad adicional de la presente invención es proveer composiciones para tratar o prevenir obesidad y enfermedades relacionadas en un sujeto comprendiendo una cantidad efectiva de por lo menos un compuesto de la invención.

Estos y otros objetos de la invención serán claros en vista de la siguiente descripción detallada.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La invención se refiere a derivados de ácido bifenil-4-il carbonilamino y sales y ésteres farmacéuticas de los mismos, que tienen utilidad en la inhibición de DGAT-1 (diacilglicerol O-aciltransferasa tipo 1) y en el tratamiento de obesidad y enfermedades relacionadas.

Una modalidad de la invención es un compuesto de la Fórmula (I)



(I)

en donde

Q es O, NR^{11}, o S;

(A) es un anillo fusionado seleccionado de un anillo aromático de 6 miembros conteniendo 0 ó 1 átomos de N;

R^1 es independientemente seleccionado de halo, alquilo de (C_1-C_6), alcoxi de (C_1-C_6), nitro, ciano, haloalquilo de (C_1-C_6), haloalcoxi de (C_1-C_6), aminocarbonilo, alquilaminocarbonilo de (C_1-C_6), bis{alquilo(C_1-C_6)] aminocarbonilo, aminosulfonilo, alquilaminosulfonilo de (C_1-C_6), bis[alquilo de (C_1-C_6)] aminosulfonilo, alquilcarbonilamino de (C_1-C_6), alquilsulfonilo de (C_1-C_6), alquilsulfonilamino de (C_1-C_6), hidroxi-alquilaminocarbonilo de (C_2-C_6), 1-morfolinilcarbonilo, y 1-piperidinilcarbonilo, y Cuando dos de dichos sustituyentes de R^1 son alquilo de (C_1-C_6), y se unen a átomos de carbono

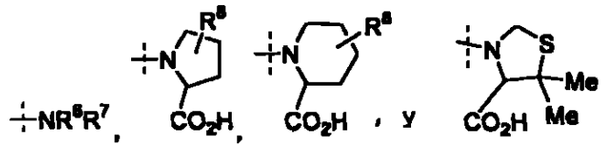
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adyacentes del Anillo A, pueden unirse para formar un anillo carbociclico de 5-7 miembros;

n es 0, 1, ó 2;

R^2 y R^3 se seleccionan independientemente de hidrógeno, halo, hidroxi, alquilo de (C_1-C_6), trifluorometilo, alcoxi de (C_1-C_6), y trifluorometoxi;

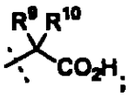
R^4 se selecciona de



en donde:

R^6 es H o CH_3;

y

R^7 es  ;

en donde

R^9 se selecciona de

Alquilo de (C_1-C_6) opcionalmente sustituido con uno o dos grupos seleccionados de vinilo, CF_3, OH, metoxi, SCH_3, NH_2, $-CO_2H$, y $-CONH_2$,

Fenilo de $(CH_2)_m$ en donde m es de 0 a 3, y

en donde el anillo de fenilo es opcionalmente sustituido con uno o

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dos grupos seleccionados de halo, alquilo de (C_1-C_6), alcoxi de (C_1-C_6), OH, nitro y ciano,

piperidinilo opcionalmente sustituido en C con halo y opcionalmente sustituido con C o N con alquilo de (C_1-C_6), alcoxi de (C_1-C_6), nitro, o ciano,

tetrahidropiran-4-ilo;

R^{10} es H o metilo;

o

R^9 y R^{10} pueden formar, junto con el carbono al que se unen, un anillo carbocíclico de 3 a 6 miembros,

R^8 es hidrógeno, alquilo de (C_1-C_6), hidroxi o metoxi;

R^5 se selecciona de H, alquilo de (C_1-C_6), e hidroxi-alquilo de (C_2-C_6);

R^{11} se selecciona de H, alquilo de (C_1-C_6), e hidroxi-alquilo de (C_2-C_6);

y sales y ésteres farmacéuticamente aceptables de los mismos.

Los términos identificados arriba tienen el siguiente significado durante toda la patente:

El término "halo" significa F, Br, Cl, e I.

Los términos "alquilo de (C_1-C_4)", "alquilo de (C_1-C_6)", y "alquilo de (C_2-C_6)" significan grupos hidrocarburo saturados lineales o ramificados que tienen de 1 a aproximadamente 4 átomos de carbono, de 1 a aproximadamente 6 átomos de carbono o de 2 a aproximadamente 6 átomos de carbono, respectivamente. El grupo hidrocarburo también puede incluir un fragmento de alquilo cíclico como parte del grupo alquilo. Dichos grupos incluyen, pero no están limitados a, grupos metilo, etilo, n-propilo, isopropilo, butilo, isobutilo, pentilo, hexilo, ciclopropilo, ciclohexilo, ciclopropil-metilo, y ciclopentil-metilo.

El término "alcoxi de (C_1-C_6)" significa un grupo hidrocarburo saturado lineal o ramificado que tiene de 1 a aproximadamente 6 átomos de carbono, dicho grupo estando unida a un átomo de oxígeno. El átomo de oxígeno es el átomo a través del cual se une el sustituyente alcoxi al resto de la molécula. El grupo hidrocarburo también puede incluir un fragmento de alquilo cíclico como parte del grupo alquilo. Dichos grupos incluyen, pero no están limitados a, metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi, n-hexiloxi, 3,3-dimetilpropoxi, ciclopropoxi, ciclopropilmetoxi, ciclopentiloxi, y similares.

El término "haloalcoxi de (C_1-C_6)" significa un grupo alcoxi de (C_1-C_6) sustituido en carbono con un átomo de halógeno. Dichos grupos incluyen, por ejemplo,

trifluorometoxi, difluorometoxi, 2,2-difluoroetoxi, 2,2,2-trifluoroetoxi, 3-fluoropropoxi, 2-cloroetoxi, 3-cloropropoxi, 1-fluoro-2,2-dicloroetoxi y similares.

El término "haloalquilo de (C_1-C_6)" significa un grupo alquilo de (C_1-C_6) sustituido en carbono con un átomo de halógeno. Dichos grupos incluyen, por ejemplo, trifluorometilo, difluorometilo, 2,2,2-trifluoroetilo, 3-fluoropropilo, difluoroetilo, 1-fluoro-2,2-dicloroetilo, 3-cloropropilo, 4-bromohexilo y similares.

Los términos "aminocarbonilo", "alquilaminocarbonilo de (C_1-C_6)", y "bis[alquilo de (C_1-C_6)]aminocarbonilo" significa un grupo carbonilo de [C(=O)] sustituido por átomo de nitrógeno en el cual no se sustituye el átomo de nitrógeno, sustituido por un solo grupo alquilo de (C_1-C_6), respectivamente. El grupo carbonilo es el unto de unión del sustituyente para le resto de la molécula. Dichos grupos incluyen, por ejemplo, carboxiamido [$NH_2C(=O)$-], N-metilcarboxiamido [$CH_3NHC(=O)$], *N*-metil-*N*-propilcarboxiamido [$CH_3CH_2CH_2N(CH_3)C(=O)$-], *N,N*-dietoxicarboxiamido [$(CH_3CH_2)_2NC(=O)$-], y similares.

Los términos "anillo carboxíclico de 3 a 6 miembros" y "anillo carbocíclico de 5 a 7 miembros" significan un anillo saturado o parcialmente insaturado que contiene de aproximadamente 3 a alrededor de 6 átomos de carbono, y de aproximadamente 5 a alrededor de 7 átomos de

carbono, respectivamente. Dichos grupos incluyen, pero no están limitados a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentenilo, ciclohexenilo y similares.

El término "hidroxi-alquilo de (C_2-C_6)" significa un grupo alquilo de (C_2-C_6), dicho alquilo siendo sustituido además por un grupo hidroxi en cualquier átomo de carbono disponible. Dichos grupos incluyen, pero no están limitados a, hidroximetilo, 2-hidroxietilo, 2-hidroxipropilo, 3-hidroxipropilo, 4-hidroxibutilo, 2-hidroxi-1-metiletilo, 5-hidroxipentilo, 3-hidroxibutilo, 3-hidroxi-2-etilpropilo, 6-hidroxihexilo y similares.

El término "hidroxi-alquilaminocarbonilo de (C_2-C_6)" significa un grupo carbonilo [C(=O)] sustituido por átomo de nitrógeno en el cual el átomo de nitrógeno se sustituye por un solo grupo alquilo de (C_2-C_6), y dicho alquilo además es sustituido por un grupo hidroxi. Dichos grupos incluyen, por ejemplo, 2-hidroxietilamido-, 3-hidroxipropilamido, 4-hidroxihexilamido, y similares.

Los términos "aminosulfonilo", alquilaminosulfonilo de (C_1-C_6)", y "aminosulfonilo de bis[alquilo de (C_1-C_6)]" significa un grupo de $S(=O)_2$ sustituido por átomo de nitrógeno en el cual el átomo de nitrógeno es no sustituido, sustituido por un solo grupo alquilo de (C_1-C_6), o por dos grupos alquilo de (C_1-C_6), respectivamente. El grupo de $S(=O)_2$

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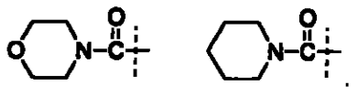
es el punto de unión del sustituyente al resto de la molécula. El grupo de $S(=O)_2$ es el punto de unión del sustituyente al resto de la molécula. Dichos grupos incluyen, por ejemplo, aminosulfonil [$NH_2S(=O)_2$-], N-metilaminosulfonil- [$CH_3NHS(=O)_2$], N-metil-N-propilaminosulfonil [$CH_3CH_2CH_2N(CH_3)S(=O)_2$-], N,N-dietilaminosulfonil [$(CH_3CH_2)_2NS(=O)_2$-] y similares.

El término "alquilcarbonilamino de (C_1-C_6)" significa un grupo amino en el cual el átomo de nitrógeno se sustituye por un grupo carbonilo, y dicho grupo carbonilo además se sustituye por un grupo alquilo de (C_1-C_6). El átomo de nitrógeno es el punto de unión del sustituyente al resto de la molécula. Dichos grupos incluyen, por ejemplo, grupos acetilamino [$CH_3C(=O)NH$-], propanoilamino [CH_3CH_2C $(=O)NH$-], *i*-butanoilamino [$(CH_3)_2CHC(=O)NH$-], y similares.

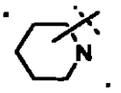
El término "alquilsulfonilamino de (C_1-C_6)" significa un grupo amino en el cual el átomo de nitrógeno se sustituye por un gruo sulfonilo [$S(=O)_2$], y dicho grupo sulfonilo se sustituye además por un grupo alquilo (C_1-C_6). El átomo de nitrógeno es el punto de unión del sustituyente al resto de la molécula. Dichos grupos incluye, por ejemplo, metilsulfonilamino [$CH_3S(=O)_2NH$-], propilsulfonilamino [$CH_3CH_2CH_2S(=O)_2NH$-], *i*-propilsulfonilamino [$(CH_3)_2CHS(=O)_2NH$-], y similares.

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Los términos "1-morfolinilcarbonilo" y "1-piperidinilcarbonilo" significa



, respectivamente.

El término "piperidinilo" significa  . El punto de unión de este sustituyente puede ser ya sea N o cualquier átomo de C en el anillo.

El término "opcionalmente sustituido" significa que la porción así modificada puede tener de ninguno hasta por lo menos el número superior de sustituyentes indicados. Cada sustituyente puede reemplazar cualquier átomo de hidrógeno en la porción así modificada mientras que el reemplazo es químicamente posible y químicamente estable. Cuando hay dos o más sustituyentes en cualquier porción, cada sustituyente se elige independientemente de cualquier otro sustituyente y, consecuentemente, puede ser igual o diferente.

Las abreviaturas del fragmento de aminoácidos normales (v.gr., Val, Leu, Ile, Pro, y similares) se usan en las siguientes Tablas para describir un fragmento de aminoácidos bivalente. Se deberá entender que los puntos de unión del fragmento bivalente son a través del átomo de nitrógeno del fragmento y el átomo de carbono del grupo carbonilo. Por ejemplo, en la Tabla 1a, el fragmento se une a la molécula a través del átomo de nitrógeno y se sustituye en

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el C(=O) con un grupo OH. Como se introduce en la tabla, el punto de unión al resto de la molécula es en la izquierda, y el grupo OH está en la derecha. También se deberá entender que cuando se designa el fragmento como "L", su configuración absoluta es la de los aminoácidos presentes en la naturaleza; mientras que la designación "D" tiene la configuración absoluta opuesta.

Los compuestos descritos en los Ejemplos se pretende que sean representativos de la invención, y se entenderá que el alcance de la invención no se limita por el alcance de los ejemplo. Aquellos expertos en la materia reconocerán que la invención puede practicarse con variaciones en las estructuras, materiales, composiciones y métodos descritos y dichas variaciones se consideran dentro del ámbito de la invención.

Las sales respectivas de los compuestos de la Fórmula (I) incluyen las sales convencionales no tóxicas y las sales de amonio cuaternario que se forman, por ejemplo, de ácidos o bases inorgánicas u orgánicas por medios bien conocidos en la materia. Por ejemplo, dichas sales de adición de ácidos incluyen acetato, adipato, alginato, ascorbato, aspartato, benzoato, bencensulfonato, bisulfato, butirato, citrato, alcanforato, alcanforsulfonato, cinamato, ciclopentanopropionato, digluconato, dodecilsulfato, etansulfonato, fumarato, glucoheptanoato, glicerofosfato,

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hemisulfato, heptanoato, hexanoato, clorhidrato, bromhidrato, yodhidrato, 2-hidroxietansulfonato, itaconato, lactato, maleato, mandelato, metansulfonato, 2-naftalensulfonato, nicotinato, nitrato, oxalato, pamoato, pectinato, persulfato, 3-fenilpropionato, picrato, pivalato, propionato, succinato, sulfonato, tartrato, tiocianato, tosilato, y undecanoato.

Las sales de base incluyen sales de metales alcalinos tales como sales de potasio y sodio, sales de metal alcalinotérreo tales como sales de calcio y magnesio, y sales de amonio con bases inorgánicas tales como sales de diciclohexilamina y N-metil-D-glucamina. Adicionalmente, los grupos básicos que contienen nitrógeno pueden cuaternizarse con dichos agentes como haluros alquilo inferiores tales como cloruros de metilo, etilo, propilo y butilo, bromuros y yoduros; sulfatos de dialquilo como sulfato de dimetilo, dietilo y dibutilo y sulfatos de diamilo: haluros de cadena larga tales como cloruros, bromuros y yoduros de decilo, laurilo, miristilo y estearilo; haluros de aralquilo como bromuros de bencilo y fenetilo y similares.

Los ésteres de la presente invención son derivados de éster no tóxicos farmacéuticamente aceptables de los compuestos de la Fórmula (I). Esto puede incluir, por ejemplo, derivados de éster preparados de ácido acético, benzóico, mandélico, esteárico, láctico, salicílico, hidroxinaftoico, glucoheptanoico y glucónico. Los compuestos

de la Fórmula (I) pueden esterificarse por una variedad de procedimientos convencionales bien conocidos por los expertos en la materia. Por ejemplo, la esterificación puede lograrse usando el ácido carboxílico apropiado en presencia de anhídrido trifluoroacético y opcionalmente, piridina o en presencia de N,N-carbonildiimidazol con piridina. Un experto en la materia podría conocer fácilmente como llevar a cabo exitosamente estos y otros métodos de esterificación. Los grupos sensitivos o reactivos del compuesto de la fórmula (I) puede necesitar ser protegido durante cualquiera de los métodos anteriores para formar ésteres y los grupos protectores pueden agregarse y removerse por métodos convencionales bien conocidos en la materia.

Se apreciará que los diaesterómeros y enantiómeros de las estructuras ejemplificadas con frecuencia serán posibles y que los isómeros puros representan una modalidad de la invención. Se pretende que los estereoisómeros puros y mezclas de los mismos estén dentro del alcance de la invención.

Los compuestos de esta invención, ya sea por naturaleza de centros asimétricos o por rotación restringida, pueden estar presentes en forma de isómeros. Cualquier isómero puede estar presente en la configuración (R), (S), o (R,S), preferiblemente en la configuración (R) o (S), cualquiera que sea más activa.

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Todos los isómeros, ya sea que estén separados, puros, parcialmente puros o en mezcla racémica, de los compuestos de esta invención son abarcados dentro del alcance de esta invención. La purificación de dichos isómeros y la separación de las mezclas isoméricas puede lograrse por técnicas normales conocidas en la materia.

Los isómeros geométricos por naturaleza de sustituyentes alrededor de un doble enlace o un anillo puede estar presente en forma cis (=Z) o trans (=E), y ambas formas isoméricas se abarcan dentro del alcance de esta invención.

El proceso particular que será utilizado en la preparación de los compuestos de esta invención depende del compuesto específico deseado. Dichos factores como la selección de las porciones específicas y los sustituyentes específicos den las diferentes porciones, todos juegan un papel en la trayectoria que será seguida en la preparación de los compuestos específicos de esta invención. Estos factores se reconocen fácilmente por alguien con experiencia ordinaria en la materia.

Para síntesis de cualquier compuesto particular, alguien con experiencia en la materia reconocerá que el uso de grupos protectores puede requerirse para la síntesis de compuestos que contienen ciertos sustituyentes. Una descripción de grupos protectores adecuados y métodos apropiados para agregar y remover dichos grupos pueden

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encontrarse en la materia (ver, por ejemplo T. W. Greene y P.G.M. Wuts, *Protective Groups in Organic Synthesis*; Wiley: New York, (1999)).

En los siguientes esquemas de reacción, alguien experto en la materia reconocerá que los reactivos y solventes realmente usados pueden seleccionarse de vario reactivos y solventes bien conocidos en la técnica por ser equivalentes efectivos. Por lo tanto, cuando reactivos o solventes específicos se muestran en un esquema de reacción, se entiende que son ejemplos ilustrativos de condiciones convenientes para ejecutar dicho esquema de reacción particular. Las abreviaturas no identificadas en el texto anexo se listan después en esta descripción bajo "Abreviaturas y Acrónimos".

Otro objeto de esta invención es proveer métodos para formar los compuestos de la invención. Los compuestos pueden prepararse de materiales fácilmente disponibles por los métodos descritos en los Esquemas de Reacción y Ejemplos siguientes, y por modificaciones obvias a los mismos.

Preparación General de Compuestos de la Invención

La preparación de derivados de ácido bifenil-4-il-carbonilamino de la presente invención, que tienen la fórmula (I) puede lograrse por los Métodos y Esquemas de Reacción

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descritos más adelante. Los métodos para la preparación de compuestos específicos teniendo la Fórmula (II), (III), (IV), (VI), (XI), (XII) y (XIII) también se describen más adelante en los siguientes procedimientos experimentales.

Los compuestos de la Fórmula (V) en donde 'A' es una porción benzo se pueden preparar mediante los métodos descritos en PCT/US04/14036 y por otros métodos conocidos en la materia, tales como los siguientes: (a) 2-cloro-5-cianobenzotiazol y 2-cloro-6-cianobenzotiazol (WO 2002/000633); (b) 5-acetamido-2-clorobenzotiazol (Sharpe y otros, J. Med. Chem. 15: 523-529, 1972); (c) 6-acetamido-2-clorobenzotiazol (Katz, J. Am. Chem. Soc. 73: 4007-4010, 1951); (d) 2-cloro-5-benzotiazol-carboxiamida, 2-cloro-N-metil-6-benzotiazolcarboxiamida, 2-cloro-N-etil-5-benzotiazol-carboxiamida, 2-cloro-N-metil-6-benzotiazolcarboxiamida, 2-cloro-N-etil-5-benzotiazol-carboxiamida, 2-N,N-dimetil-5-benzotiazolcarboxiamida, 2-cloro-N,N-dimetil-6-benzotiazolcarboxiamida, 2-Cloro-N-(2-hidroxietil)-5-benzotiazolcarboxiamida, 2-cloro-N-(2-hidroxietil)-6-benzotiazolcarboxiamida, y 2—cloro-7-morfolinocarbonil-benzotiazol (Patente de E.U.A. No. 3,654,296); (e) 6-butoxi-2-clorobenzotiazol (Bordi, y otros, Pharmaco 49; 153-166, 1994); (f) 2-cloro-6-isopropoxi-benzotiazol, 2-cloro-5-ciano-benzoxazol, y 5-ciano-2-metiltiobenzotiazol (Solicitud de Patente Europea EP

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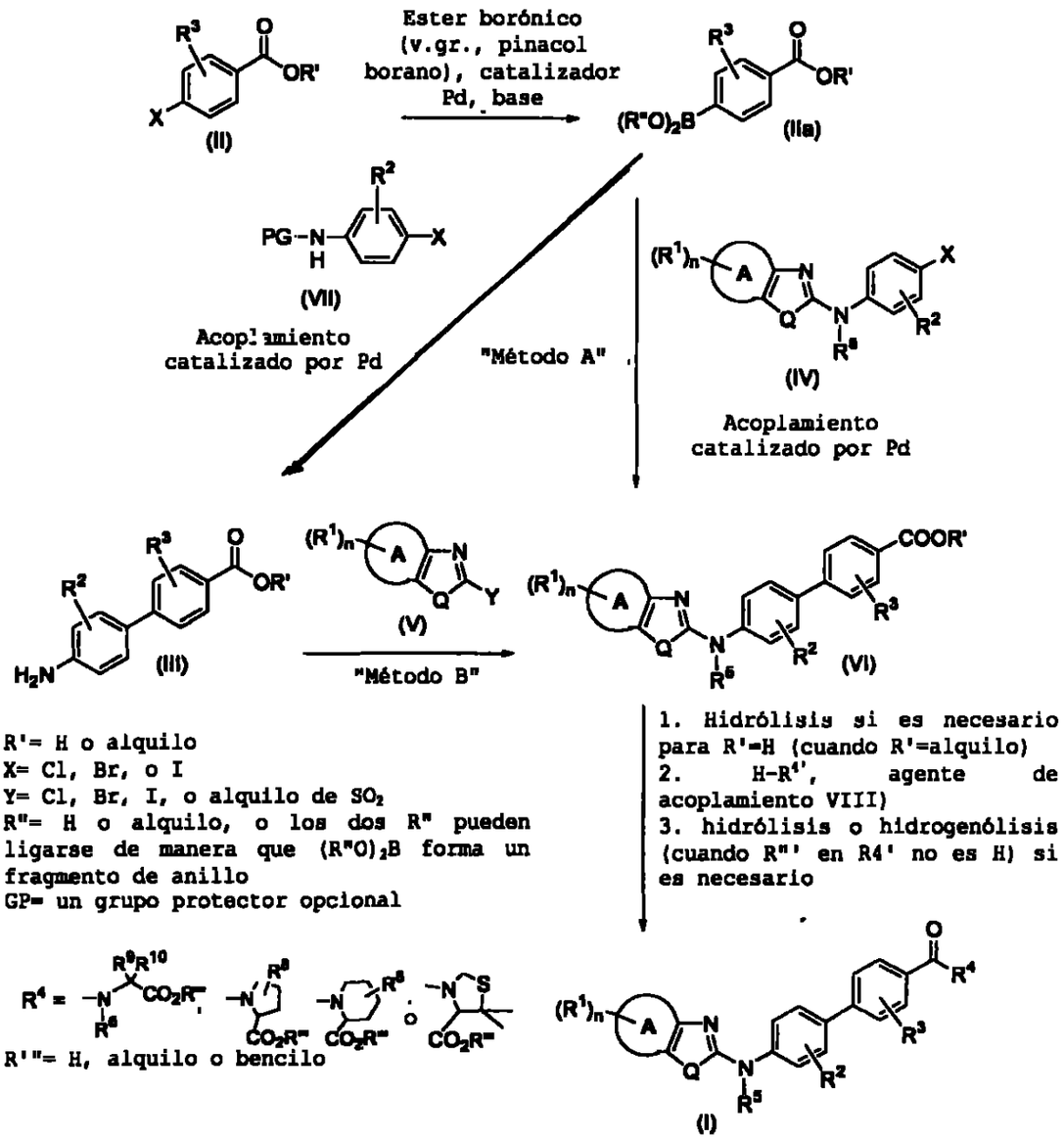
1308439A1); (g) 2-cloro-5-cianobenzoxazol (Solicitud de Patente Europea EP1308439A1). Los compuestos de la Fórmula (V) en donde 'A' es una porción heteroarilo tal como una porción pirido o pirimido puede prepararse por métodos conocidos en la materia, tal como la descrita por los siguientes compuestos e intermediarios relacionados de la Fórmula (V): (a) 2-cloro[1,3]tiazolo[4,5-b]piridina (Viviani, y otros, Bull. Soc. Chim. Fr. 130:395-404, 1993); (b) 2-cloro-5-metil[1,3]tiazolo[4,5-b]piridina (Patente de E.U.A. No. 5,496,816); (c) [1,3]tiazolo[[5,4-c]piridina-2-tiol y [1,3]tiazolo[4,5-c]piridina-2-tiol (Patente de E.U.A. NO. 5,077,287); (d) [1,3]tiazolo [5,4-c]piridina-2-tiol y [1,3]tiazolo[4,5-c]piridina-2-tiol (WO 2003/039258); y (e) 6-cloro[1,3]tiazolo[4,5-b]piridina-2-tiol (WO 2003/006470).

A menos que se especifique de otra manera, Q,A, y R^1-R^{11} tienen los significados idénticos como se describió antes.

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Esquema de Reacción 1

Métodos A y B



R'= H o alquilo
X= Cl, Br, o I
Y= Cl, Br, I, o alquilo de SO_2
R"= H o alquilo, o los dos R" pueden ligarse de manera que $(R"O)_2B$ forma un fragmento de anillo
GP= un grupo protector opcional

R^4 =

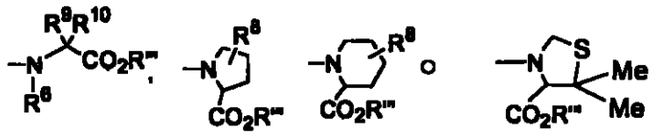
R'"= H, alquilo o bencilo

1. Hidrólisis si es necesario para R'=H (cuando R'=alquilo)
2. H-$R^{4'}$, agente de acoplamiento VIII)
3. hidrólisis o hidrogenólisis (cuando R"' en R4' no es H) si es necesario

En el Esquema de Reacción I, se preparó un derivado de éster borónico de la Fórmula (IIa) por reacción del compuesto de la Fórmula (II), en done X = halo, un catalizador de Pd, y un éster borónico (v.gr., pinacol borano). El compuesto de la Fórmula (VI) puede prepararse entonces por El "Método A" acoplando el compuesto de la Fórmula (IIa), con el compuesto de la Fórmula (IV) en presencia de un catalizador de paladio en una base tal como carbonato de potasio (condiciones Suzuki).

Alternativamente, los compuestos de la Fórmula (IIa) pueden acoplarse con una anilina de la Fórmula VII), también bajo condiciones Suzuki, para proveer el compuesto de la Fórmula (III). El compuesto de la Fórmula (VI) entonces puede prepararse por el método B, por reacción del compuesto de la Fórmula (III) con el compuesto de la Fórmula (V), en la presencia opcional de un catalizador de ácido (v.gr., HCl).

La reacción adicional del compuesto de la Fórmula (VI), en donde R' es H, con un derivado de aminoácido de la Fórmula (VIII), en donde $R^{4'}$ es



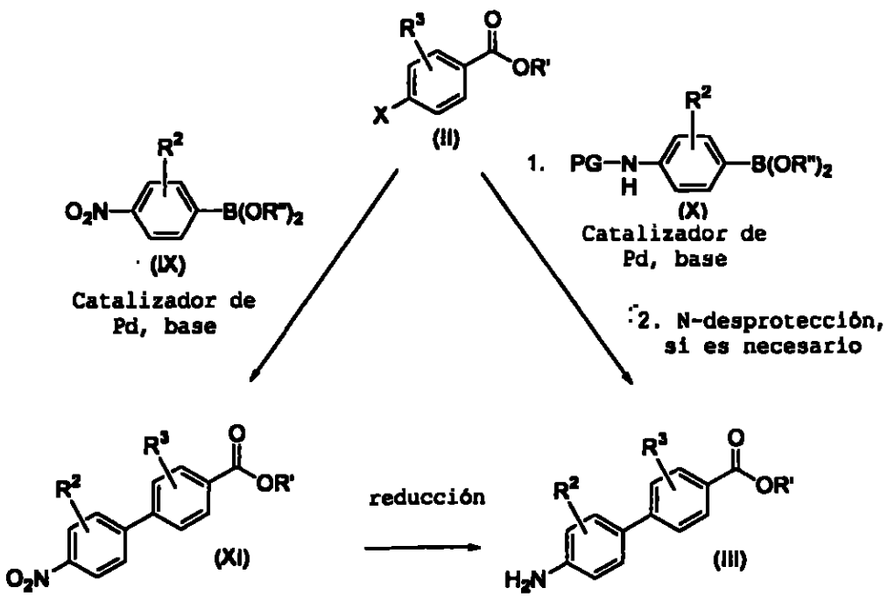
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en la presencia opcional de un agente de acoplamiento tal como N,N'-diisopropilcarbodiimida, provee un intermediario que se hidroliza (en donde R"' es alquilo) bajo condiciones básicas tales como LiOH, THF, y agua, o se hidrogena (en donde R'" es bencilo) usando H_2 y un catalizador adecuado, para dar el compuesto de la invención de la Fórmula (I).

El intermediario de la Fórmula (III), usado en el Método B, también se puede preparar por los métodos alternativos descritos en el Esquema de Reacción 2.

Esquema de Reacción 2

Métodos Alternos para la Preparación de (III)



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R'= H o alquilo

X= Cl, Br, o I

Y= Cl, Br, I, o alquilo de SO_2

R"= H o alquilo, o los dos R" pueden ligarse de manera que $(R"O)_2B$ forma un fragmento de anillo

GP= un grupo protector opcional

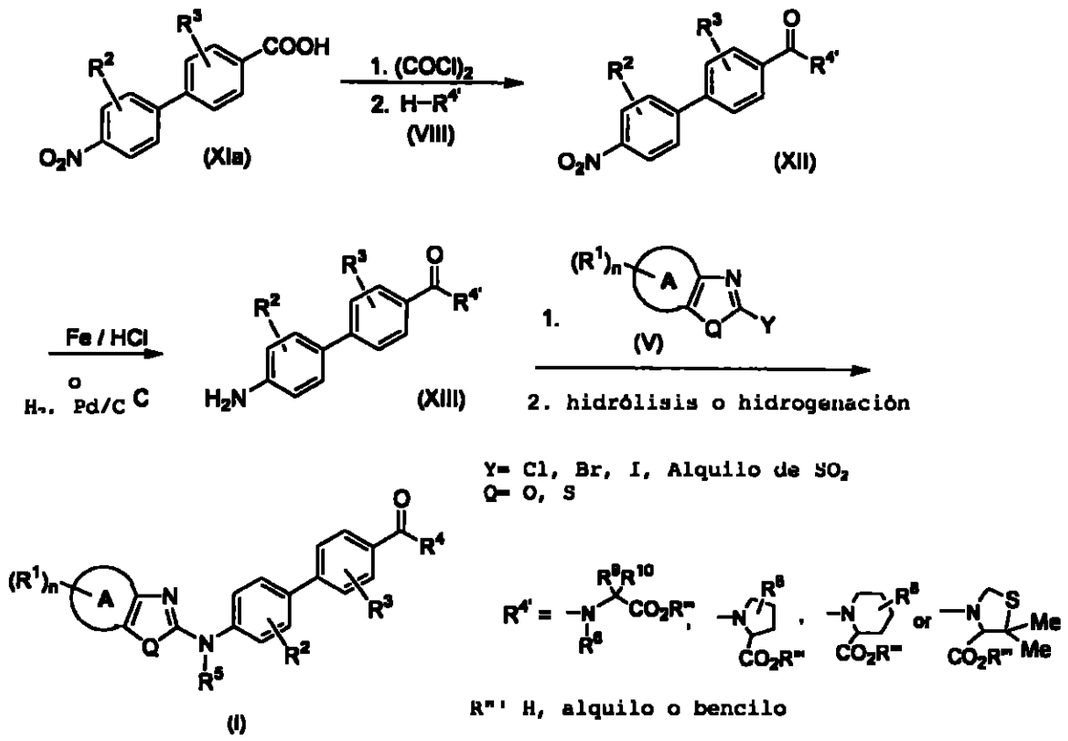
Por ejemplo, el compuesto de la Fórmula (II) puede acoplarse con un derivado de ácido nitrofenilborónico de la Fórmula (IX) bajo condiciones Suzuki (catalizador de Pd y base) para dar el compuesto de la Fórmula (XI). Reducción del intermediario de la Fórmula (XI) (v.gr., H_2 Pd/C o Fe/HCl) da el compuesto aminobifenilo de la Fórmula (III). Alternativamente, el compuesto de la Fórmula (II) puede acoplarse con un derivado de ácido aminoborónico protegido de la Fórmula (X), para dar, la siguiente remoción del grupo protector, el intermediario de la Fórmula (III).

La preparación de los compuestos de la Fórmula (I) también se puede lograr por el Método C, como se ilustra en el Esquema de Reacción 3.

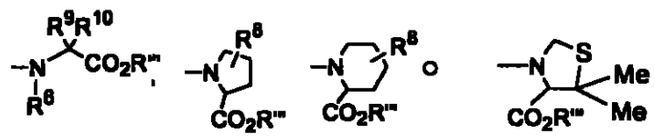
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Esquema de Reacción 3

Método C



En esta ruta, un compuesto de nitrobifenilo de la Fórmula (XIa) se convierte al compuesto de la Fórmula (XII) por conversión de (XIa) al cloruro de ácido correspondiente (v.gr., usando $(COCl)_2$) seguido por acoplamiento con el derivado de amincácido de la Fórmula (VIII), en donde $R^{4'}$ es

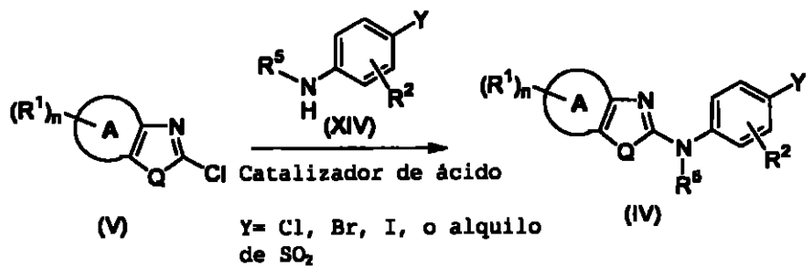


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En presencia opcional de una base. Alternativamente, el compuesto de la Fórmula (XII) puede prepararse haciendo reaccionar (XIa) y (VIII) en presencia de un agente de acoplamiento tal como diciclohexilcarbodiimida u otros agentes de acoplamiento normales. El grupo nitro en el compuesto de la Fórmula (XII) luego se reduce con, por ejemplo, H_2 y Rd/C o Fe/HCl, para producir el compuesto intermediario de la Fórmula (XIII). La reacción de (XIII) con el compuesto de la Fórmula (V) en presencia de un catalizador de ácido (v.gr., HCl) seguido por hidrólisis o hidrogenación como en el Esquema de Reacción I, da el compuesto de al invención de la Fórmula (I).

Los compuestos de la Fórmula (IV) se preparan como se ilustra en el Esquema de Reacción 4, por reacción una anilina de la Fórmula (XIV) con el intermediario de la Fórmula (V), por ejemplo, bajo condiciones de ácido (v.gr., HCl en n-butanol) a 90°C.

Esquema de Reacción 4



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Las modalidades específicas de la invención pueden encontrarse en los Ejemplos descritos más adelante y en las Tablas 1-7. Los compuestos descritos en estos Ejemplos y Tablas se pretende que representan la invención y se entenderá que el alcance de la invención no se limite por el alcance de los ejemplos. Los expertos en la materia reconocerán que la invención sea practicada con variaciones en las estructuras, materiales, composiciones y métodos descritos y dichas variaciones están dentro del ámbito de la invención.

PREPARACIÓN DE COMPUESTOS DE LA INVENCIÓN

Espectros de Masas

Se obtuvieron espectros de masa de ionización química (EM-IQ) con un espectrómetro de masas Hewlett Packard 5989A equipado con un Cromatógrafo de Gases de Hewlett Packard 5890 con una columna J&W DB-5 (revestimiento de 0.25 uM; 30 m x 0.25 mm). La fuente de iones se mantuvo a 250°C y los espectros se escanearon de 50-800 amu a 2 seg por escaneado.

Se obtuvieron datos de espectros de masa por cromatografía de líquidos-electro rociado (EM-CL) usando un CLAR Hewlett-Packard 1100 equipado con una bomba cuaternaria,

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un detector de longitud de onda variable fijado a 254 nm, una columna de C-18 YMC por (2X3 mm, 120A), y un espectrómetro de masas de trampa de iones Finnigan LCQ con ionización de electro rociado. Se escanearon espectros de 120-1200 amu usando un tiempo de iones variable de acuerdo con el número de iones en la fuente. Los eluyentes fueron A: 2% acetonitrilo en agua con 0.02% TFA, y B: 2% agua en acetonitrilo con 0.018% TFA. La elusión de gradiente de 10% B a 95% B durante 3.5 minutos a un régimen de flujo de 1.0 ml/min se usó con un control inicial de 0.5 minutos y un control final de 0.5 minutos a 95% B. El tiempo de operación total fue de 6.5 minutos. En los Ejemplo y Tablas provistos más adelante, se dan datos de EM-CL con tiempos de retención (tiempo de ret.) de CLAR.

Espectros de RMN

Se realizó espectroscopia de RMN de una dimensión de rutina en espectrómetros Varian Mercury-plus de 300 MHz o 400 MHz. Las muestras se disolvieron en solventes deuterados obtenidos de Cambridge Isotope Labs y se transfirieron a tubos de RMN ID Wildmad de 5 mm. Los espectros se adquirieron a 19.85°C. Los cambios químicos se registraron en escala de ppm y se hace referencia a ellos a las señales de solventes apropiadas, tales como 2.49 ppm para DMSO-d_6, 1.93 ppm para

CD_3CN, 3.30 ppm para CD_3OD, 5.32 ppm para CD_2Cl_2 y 7.26 ppm para $CDCl_3$ para espectros de ^1H; y 39.5 ppm para DMSO-d_6, 1.3 ppm para CD_3CN, 49.0 ppm para CD_3OD, 53.8 ppm para DC_2Cl^2 y 77.0 ppm para $CDCl_3$ para espectros de ^{13}C.

Abreviaturas y Acrónimos

Cuando se usan las siguientes abreviaturas a través de esta descripción, tienen el siguiente significado:

Ala	alanina
Biotage®	cromatografía de gel de sílice de presión media, usando aparatos de Biotage Inc./Dyax Corp.
$CDCl_3$	cloroformo deuterado
Celite®	agente de filtro de tierra diatomacea, obtenido de Celite Corp.
DCE	Dicloroetano
DCM	diclorometano
DMF	N,N-dimetilformamida
DMSO	sulfóxido de dimetilo
ee	exceso enantiomérico
EI-MS	cromatografía de líquidos de alta presión
h	horas
CLAR	cromatografía de líquidos de alta presión
Ile	isoleucina

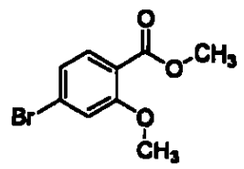
EM-CL	cromatografía de líquidos-espectroscopía de masas
Leu	leucina
Min	minutos
EM	Espectroscopía de masas
RMN	resonancia magnética nuclear
Phe	fenilalanina
p.o.	oralmente
Pro	prolina
ta	temperatura ambiente
THF	tetrahidrofurano
CLF	Cromatografía de capa fina
ATF	ácido trifluoroacético
Val	valina

Usando los métodos descritos en la presente, se pueden preparar los compuestos de la presente invención. Se presentaron los siguientes ejemplos para ilustrar más la invención descrita en la presente pero no se deberán interpretar como limitantes del alcance de la invención de ninguna manera.

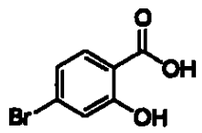
Preparación de Intermediarios

Compuestos de la Fórmula (II)

Intermediario II-1: 4-bromo-2-metoxibenzoato de metilo



Paso 1. Preparación de ácido 4-bromo-2-hiroxibenzoico

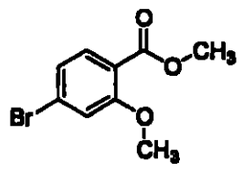


Se agregó nitrito de t-butilo (5.10 g, 49.5 mmoles) a una suspensión de bromuro de cobre (II) (8.80 g, 39.4 mmoles) en CH_3CN (50 ml), y la mezcla de reacción se enfrió a 0°C en un baño de hielo. Se agregó ácido 4-aminosalicílico (5.00 g, 32.7 mmoles) en pequeñas porciones durante 30 minutos. Se agregó CH_3CN adicional (20 ml), y la mezcla de reacción se dejó agitar a 0°C durante 2 h. La mezcla de reacción se vertió en HCl al 20% (200 ml) y se extrajo con Et_2O (2 x 200 ml). Las fases orgánicas combinadas se lavaron con 20% HCl (2 x 100 ml), se secó sobre $MgSO_4$, se filtró y se

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concentró a vacío. El residuo se disolvió en Et_2O (300 ml) y se extrajo con 10% de NaOH (2 x 150 ml). Las capas acuosas combinadas se lavaron con Et_2O (100 ml), se llevó a pH ~1 con 20% HCl, y se extrajo con Et_2O (3 x 200 ml). Las fases orgánicas combinadas se secaron sobre $MgSO_4$, se filtró, y se concentró a vacío. El sólido resultante se trituró con $CHCl_3$ y se recopiló por filtración, dando 2.5 g (35%) del compuesto del título como un sólido cristalino. El material se usó sin caracterización o purificación adicional.

Paso 2. Preparación de 4-bromo-2-metoxibenzoato de metilo

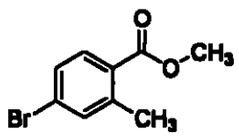


Se disolvió ácido 4-bromo-2-hidroxibenzoico (1.00 g, 4.61 mmoles) en acetona (20 ml) y se agregaron yodometano (1.15 ml, 18.4 mmoles) y K_2CO_3 (2.55 g, 18.4 mmoles). La reacción se calentó durante la noche a reflujo. Al enfriarse a ta, la mezcla de reacción se filtró y el filtrado se concentró a vacío. El material crudo se purificó por cromatografía instantánea (columna Biotage®; EtOAc al 10%/Hexanos), dando 0.955 g (85%) del producto deseado como un aceite amarillo. CL/EM m/z 245.0 (MH^+); tiempo de

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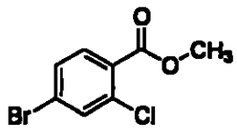
retención 3.13 min. RMN ^1H (400 MHz, CD_2Cl_2) δ 3.84 (s, 3H), 3.90 (s, 3H), 7.12-7.20 (m, 2H), 7.62 (d, 1H).

Intermediario II-2: 4-bromo-2-metilbenzoato de metilo



Se agregó ácido 4-bromo-2-metilbenzoico (2.00 g, 9.30 mmoles) a una solución de cloruro de acetilo (1.70 ml, 23.9 mmoles) en metanol (30 ml). La mezcla se dejó agitar a ta durante 3 días y luego se concentró a vacío. Esto dio 1.96 g (92%) del compuesto del título como un aceite café claro. RMN ^1H (400 MHz, CD_2Cl_2) δ 2.61 (s, 3H), 3.90 (s, 3H), 7.38-7.42 (m, 2H), 7.78 (d, 1H).

Intermediario II-3: 4-bromo-2-clorobenzoato de metilo



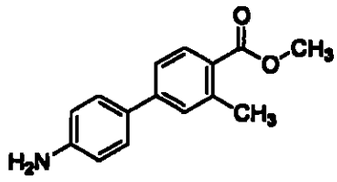
Se agregó ácido 4-bromo-2-clorobenzoico (1.00 g, 4.25 mmoles) a una solución de cloruro de acetilo (1.70 ml,

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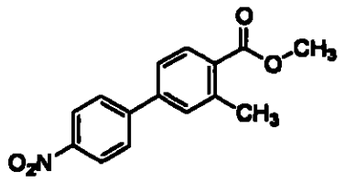
23.9 mmoles) en metanol (30 ml). La mezcla se dejó agitar a ta durante 3 días, y luego se concentró a vacio. Esto dio 0.84 g (80%) del compuesto del título. RMN ^1H (400 MHz, CD_2Cl_2) δ 3.85 (s, 3H), 7.51 (d, 1H), 7.45 (d, 1H), 7.78 (d, 1H).

Preparación de Compuestos Intermediarios de la Fórmula (III)

Intermediario III-1: 4'-amino-3-metilbifenil-4-carboxilato de metilo



Paso 1. Preparación de 3-metil-4'-nitrobifenil-4-carboxilato de metilo

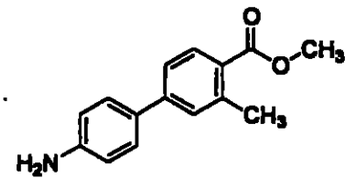


A una solución de 4-bromo-2-metilbenzoato de metilo (1.00 g, 4.37 mmoles) y ácido 4-nitrofenilborónico (2.91 g, 17.5 mmoles) en tolueno (12 ml) se le agregó Na_2CO_3 (3.70 g,

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34.9 mmoles) complejo de cloruro de 1,1'-bis(difenilfosfino)ferrocenopaladio (II) con diclorometano (0.71 g, 0.87 mmoles), 1,4-dioxano (6 ml) y agua (6 ml). La mezcla se calentó a reflujo durante 3 h y luego se dejó enfriar a ta. La mezcla se diluyó con EtOAc y agua, y la capa orgánica se aisló, se secó sobre $MgSO_4$, y se concentró a vacío. El material se purificó por cromatografía en columna (25% EtOAc en hexanos), dando 1.32 g (89%) del compuesto del título. CG/EM m/z 271 (M^+); tiempo de retención 13.00 min. RMN ^1H (400 MHz, CD_2Cl_2) δ 2.65 (s, 3H), 3.95 (s, 3H), 7.52 (d, 2H), 7.78 (d, 2H), 8.11 (d, 1H), 8.30-8.39 (m, 2H).

Paso 2: Preparación de 4'-amino-3-metilbifenol-4-carboxilato de metilo

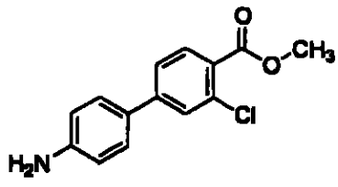


Se agregó polvo de hierro (1.04 g, 18.6 mmoles) a una solución de 3-metil-4'-nitrobifenil-4-carboxilato de metilo (0.63 g, 1.9 mmoles) en etanol (20 ml). Se agregó HCl concentrado (0.93 ml, 1.9 mmoles) y la mezcla se calentó a reflujo durante 3 h. Al enfriarse a ta, la mezcla se filtró a

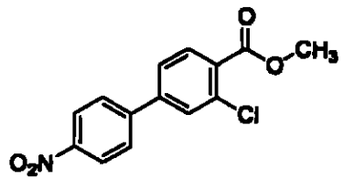
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través de una almohadilla de Celite y el filtrado se concentró a vacío. El material se purificó por cromatografía en columna (33% EtOAc en hexanos), dando 0.338 g (75%) del compuesto del título. CL/EM m/z 242.3 (MH^+); tiempo de retención 2.27 min. RMN ^1H (400 MHz, CD_2Cl_2) δ 2.81 (s, 3H), 3.95 (s, 3H), 6.83 (d, 2H), 7.41-7.51 (m, 4H), 7.85 (d, 1H).

Intermediario III-2: 4'-amino-3-clorobifenil-4-carboxilato de Metilo



Paso 1. Preparación de 3-cloro-4'-nitrobifenil-4-carboxilato de metilo

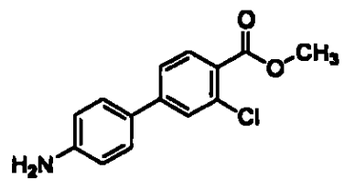


A una solución de 4-bromo-2-clorobenzoato de metilo (0.40 g, 1.6 mmoles) y ácido 4-nitrofenilborónico (0.67 g, 4.0 mmoles) en tolueno (8 ml) se le agregó Na_2CO_3 (1.02 g, 9,62 mmoles), complejo de cloruro de 1,1'-

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bis(difenilfosfino)ferrocenopaladio (II) con diclorometano (0.03 g, 0.03 mmoles), 1,4-dioxano (4 ml) y agua (4 ml). La mezcla se calentó a reflujo durante 3 h y luego se dejó enfriar a ta. La mezcla se diluyó con EtOAc y agua; y la capa orgánica se aisló, se secó sobre $MgSO_4$, y se concentró a vacío. El material se purificó por cromatografía en columna (25% EtOAc en hexanos), dando 0.275 g (59% del compuesto del título. RMN ^1H (400 MHz, CD_2Cl_2) δ 3.98 (s, 3H), 7.58 (d, 2H), 7.68-7.82 (m, 3H), 7.97 (d, 1H), 8.33 (d, 1H).

Paso 2. Preparación de 4'-amino-3-clorobifenil-4-carboxilato de metilo

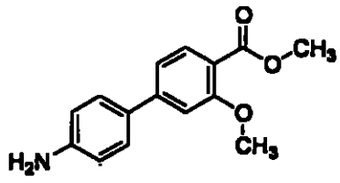


Se agregó polvo de hierro (0.99 g, 17.7 mmoles) a una solución de 3-cloro-4'-nitrobifenil-4-carboxilato de metilo (0.64 g, 1.8 mmoles) en etanol (15 ml). Se agregó HCl concentrado (0.88 ml, 1.8 mmoles) y la mezcla se calentó a reflujo durante 3 h. Al enfriarse a ta, la mezcla se filtró a través de una almohadilla de Celite®, y el filtrado se concentró a vacío. El material se purificó por cromatografía

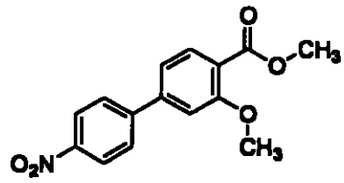
171

en columna (33% EtOAc en hexanos), dando 0.453 g (98%) del compuesto del título. CL/EM m/z 262.4 (MH^+); tiempo de retención 2.39 min. RMN ^1H (400 MHz, CD_2Cl_2) δ 3.99 (s, 3H), 6.78 (d, 2H), 7.41-7.46 (m, 3H), 7.62 (s, 1H), 7.88 (d, 1H).

Intermediario III-3: 4'-amino-3-metoxibifenil-4-carboxilato de metilo



Paso 1. Preparación de 3-metoxi-4'-nitrobifenil-4-carboxilato de metilo

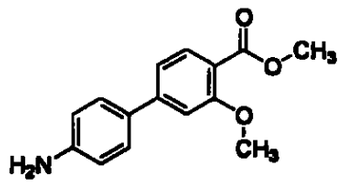


A una solución de 4-bromo-2-metoxibenzoato de metilo (0.95 g, 3.9 mmoles) y ácido 4-nitrofenilborónico (1.29 g, 7.75 mmoles) en tolueno (10 ml) se agrega Na_2CO_3 (1.85 g, 17.4 mmoles), complejo de cloruro de 1,1'-

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bis(difenilfosfino)ferrocenopaladio (II) con diclorometano (0.06 g, 0.08 mmoles), 1,4-dioxano (5 ml), y agua (5 ml). La mezcla se calentó a reflujo durante 3 h y luego se dejó enfriar a ta. La mezcla se diluyó con EtOAc y agua, y la capa orgánica se aisló, se secó sobre $MgSO_4$ y se concentró a vacío. El material se purificó por cromatografía en columna (25% EtOAc en hexanos), dando 0.675 g (61%) del compuesto del título. CL/EM m/z 287.9 (MH^+); tiempo de retención 3.14 min.

Paso 2. Preparación de 4'-amino-3-metoxibifenil-4-carboxilato de metilo



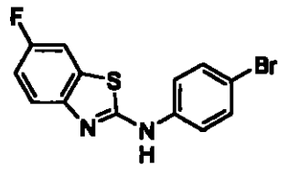
Se agregó por lo de hierro (0.58 g, 10 mmoles) a una solución de 3-metoxi-4'-nitrobifenil-4-carboxilato de metilo (0.38 g, 1.0 mmoles) en etanol (10 ml). Se agregó HCl concentrado (0.52 ml, 1.0 mmoles) y la mezcla se calentó a reflujo durante 3 h. Al enfriarse a ta, la mezcla se filtró a través de una almohadilla de Celite® y el filtrado se concentró a vacío. El material se purificó por cromatografía en columna (33% EtOAc en hexanos), dando 0.279 g (rendimiento cuantitativo) del compuesto del título. CL/EM m/z 258.3

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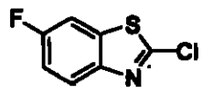
(MH$^+$); tiempo de retención 1.65 min. RMN ^{1}H (400 MHz, CD_2Cl_2) δ 3.81 (s, 3H), 3.99 (s, 3H), 6.78 (d, 2H), 7.15-7.19 (m, 2H), 7.45 (d, 2H), 7.80 (d, 1H).

Preparación de Compuestos Intermediarios de la Fórmula (IV)

Intermediario IV-I: N-(4-bromofenil)-6-fluoro-1,3-benzotiazol-2-amina



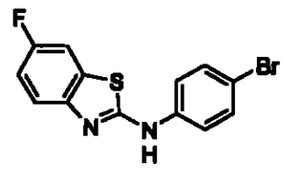
Paso 1. Preparación de 2-cloro-6-fluoro-benzotiazol



Se trató 6-fluoro-benzotiazol-2-tiol con cloruro de sulfurilo por el procedimiento descrito en PCT/US04/14036 para dar el producto deseado, que se usó en el siguiente paso sin purificación adicional. EM-IE M/z 187 (M$^+$); RMN ^{1}H (DMSO-d_6) δ 8.00 (m, 2H), 7.40 (m, 1H).

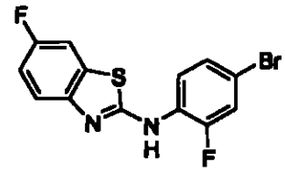
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Paso 2. Preparación de N-(4-bromofenil)-6-fluoro-1,3-benzotiazol-2-amina



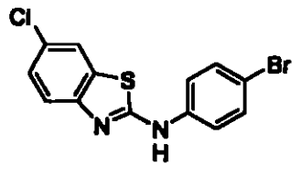
Una mezcla de 2-cloro-6-fluoro-benzotiazol (0.65 g, 3.5 mmoles) y 4-bromoanilina (0.61 g, 3.5 mmoles) en n-butanol (6 ml) se calentó a 60-70°C bajo nitrógeno para obtener una solución, al cual se le agregó lentamente por goteo HCl 4M en dioxano (0.43 ml, 1.73 mmoles). La mezcla de reacción se calentó luego a 90°C durante 18 hr. Al enfriarse a ta, la mezcla de reacción se concentró bajo presión reducida. El sólido resultante se trituró con etanol y recopiló por filtración. Esto dio 0.98 g (88%) del compuesto del título. CL/EM m/z 323.0 (MH^+); tiempo de retención 3.74 min. RMN ^1H (CD_3OD) δ 7.10-7.30 (m, 1H), 7.39 (d, 1H), 7.45 (d, 2H), 7.58-7.61 (m, 3H).

Intermediario IV-2: N-(4-bromo-2-fluoro-fenil)-6-fluoro-1,3-benzotiazol-2-amina



En una forma similar al procedimiento descrito antes para la preparación de N-(4-bromofenil)-6-fluoro-1,3-benzotiazol-2-amina, 2-cloro-6-fluorobenzotiazol y 2-fluoro-4-bromoanilina se hicieron reaccionar juntos para proveer N-(4-bromo-2-fluoro-fenil)-6-fluoro-1,3-benzotiazol-2-amina como un sólido. RMN ^{1}H RMN (DMSO-d_6) δ 10.50 (s, 1H), 8.69 (t, 1H), 7.80 (d, 1H), 7.60 (m, 2H), 7.40 (d, 1H), 7.20 (m, 1H).

Intermediario IV-3: N-(4-bromofenil)-6-cloro-1,3-benzotiazol-2-amina

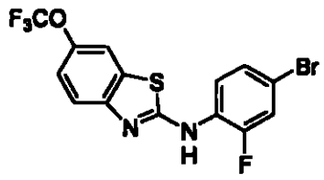


Una mezcla de 2,6-diclorobenzotiazol (0.71 g, 3.5 moles) y 4-bromoanilina (0.61 g, 3.5 mmoles) en n-butanol (6 ml) se calentó a 60-70°C bajo nitrógeno para obtener una solución, a la cual se agregó luego por goteo lentamente HCl 4M en dioxano (0.43 ml, 1.73 mmoles). La mezcla de reacción se calentó luego a 90°C durante 18 h. Al enfriarse a ta, la mezcla de reacción se concentró bajo presión reducida. El sólido resultante se trituró con etanol y se recopiló por filtración. Esto dio 1.09 g (93%) del compuesto del título.

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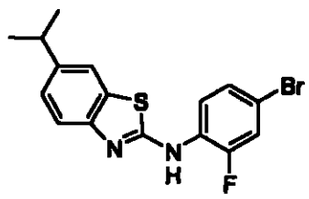
CL/EM m/z 339 (MH^+); tiempo de retención 3.98 min. RMN ^1H (CD_3OD) δ 7.31 (d, 1H), 7.42-7.58 (m, 5H), 7.61 (d, 1H).

Intermediario IV-4: N-(4-bromo-2-fluorofenil)-6-(trifluorometoxi)-1,3-benzotiazol-2-amina



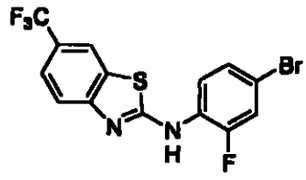
La preparación de este intermediario se describió en US 2004/0224997.

Intermediario IV-5: N-(4-bromo-2-fluorofenil)-6-isopropil-1,3-benzotiazol-2-amina



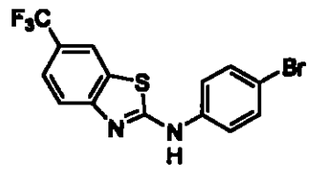
La preparación de este intermediario se describió en US 2004/0224997.

Intermediario IV-6: N-(4-bromo-2-fluorofenil)-6-(trifluorometil)-1,3-benzotiazol-2-amina



La preparación de este intermediario se describió en US 2004/0224997.

Intermediario IV-7: N-(4-bromofenil)-6-(trifluorometil)-1,3-benzotiazol-2-amina

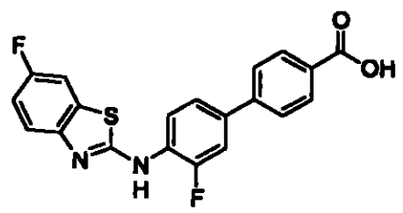


El intermediario se preparó por los métodos descritos en US 2004/0224997.

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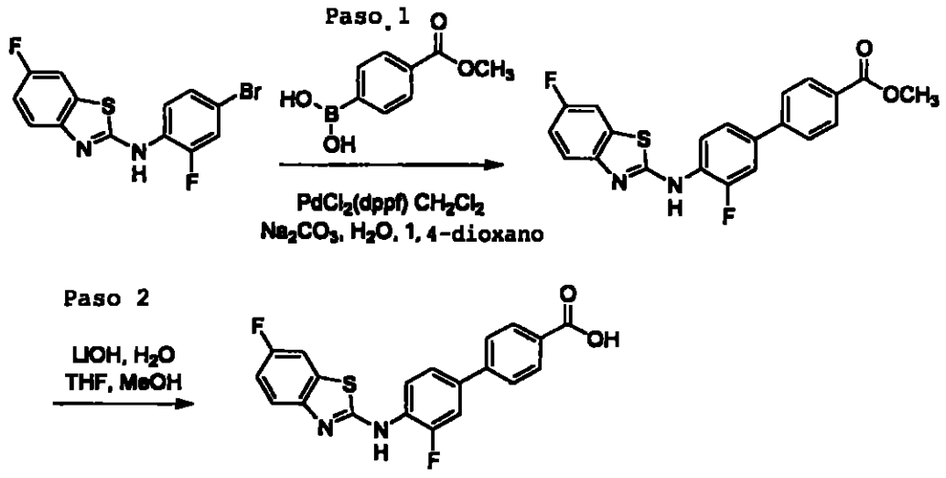
Preparación de Compuestos Intermediarios de la Fórmula (VI) por el Método A

Intermediario VI-1: Acido 3'-floro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxílico



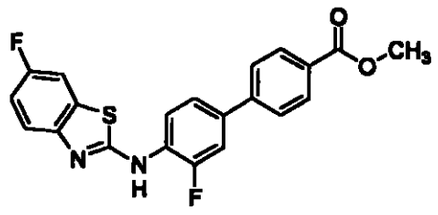
La preparación de ácido 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenol-4-carboxílico se describió más adelante en el Esquema de Reacción 5.

Esquema de Reacción 5



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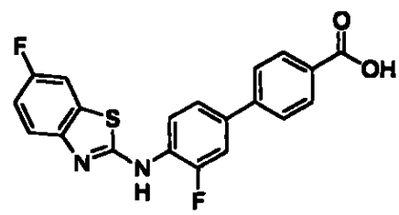
Paso 1. Preparación de 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxilato de metilo



Como se muestra en el Esquema de Reacción 5, a una mezcla de N-(4-bromo-2-fluorofenil)-6-fluoro-1,3-benzotiazol-2-amina (2.00 g, 2.93 mmoles) y ácido 4-(metoxicarbonilfenil)borónico (0.79 g, 4.40 mmoles) en tolueno (10 ml) se agregó Na_2CO_3 (1.40 g, 13.2 mmoles), complejo de cloruro 1,1'-bis(difenilfosfino) ferrocenopaladio (II) con diclorometano (0.05 g, 0.06 mmoles), 1,4-dioxano (5 ml) y agua (5 ml). Esta mezcla se calentó a reflujo durante la noche. Al enfriarse a ta, la mezcla de reacción se filtró y el sólido se lavó con agua (2 x 30 ml) y metanol (2x 30 ml). El sólido se recristalizó a partir de acetona/MeOH (2:1). Esto dio 0.641 g (55%) del producto deseado como un sólido blanquecino. RMN ^1H (400 MHz, DMSO-d_6) δ 3.82 (s, 3H), 7.20 (t, 1H), 7.59-8.02 (m, 8H), 8.70 (t, 1H), 10.50 (bs, 1H).

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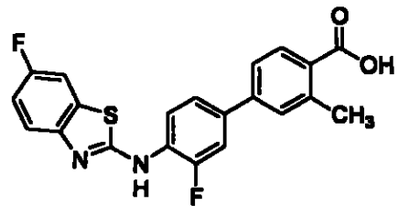
Paso 2. Preparación de ácido 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxílico



Como se muestra en el Esquema de Reacción 5, se suspendió 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxilato de metilo (0.64 g, 1.6 mmoles) se suspendió en THF (10 ml), MeOH (10 ml) y agua (5 ml) y se agregó LiOH (0.39 g, 16.2 mmoles). La mezcla de reacción se calentó a 50°C hasta que se logró disolución y luego la mezcla se agitó durante 3 días a ta. La mezcla de reacción se llevó a pH 4 con HCl 1N y se extrajo con EtOAc (3 x 25 ml). Las fases orgánicas combinadas se lavaron con agua (2 x 50 ml) y salmuera (50 ml), se secó sobre $MgSO_4$, se filtró, y se concentró a vacío. Esto dio 0.518 g (84%) del producto deseado como un sólido blanquecino. CL/EM m/z 383.3 (MH^+), tiempo de retención 3.83 min. RMN ^1H (400 MHz, DMSO-d_6) δ 7.18 (t, 1H), 7.59-8.00 (m, 8H), 8.70 (t, 1H), 10.50 (bs, 1H), 12.95 (bs, 1H).

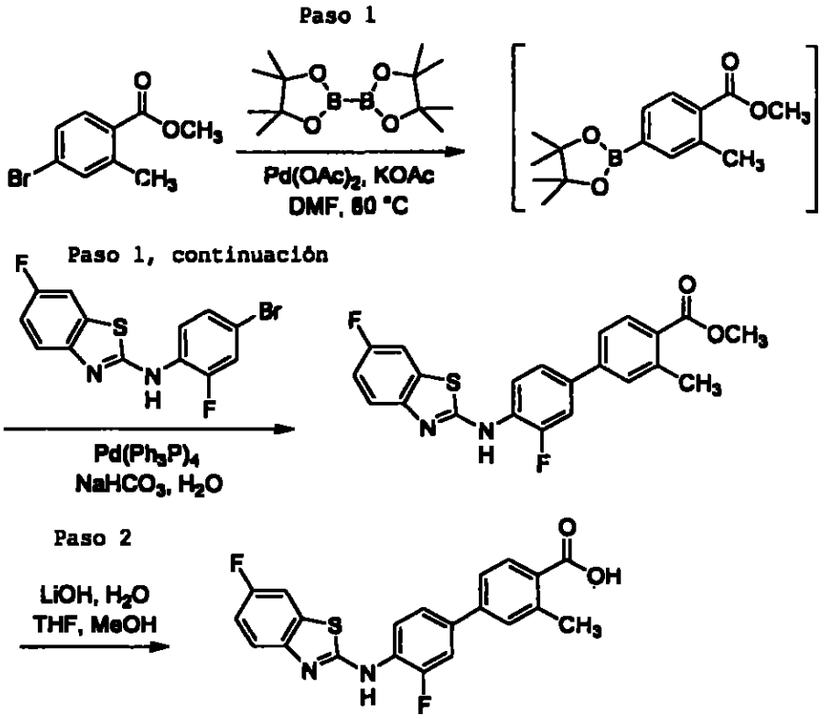
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Intermediario VI-2: ácido 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metil-bifenil-4-carboxílico



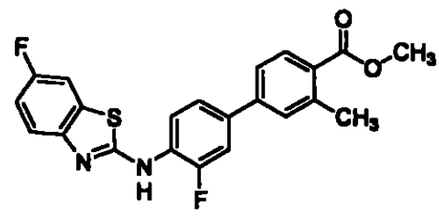
La preparación de ácido 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-carboxílico se describe más adelante en el Esquema de Reacción 6.

Esquema de Reacción 6



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Paso 1. Preparación de 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-carboxilato de metilo

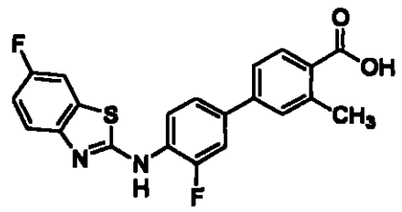


Como se muestra en el Esquema de Reacción 6, una mezcla de bis(pinacolato)diboro (0.55 g, 2.2 mmoles), 4-bromo-2-metilbenzoato de metilo (0.50 g, 2.2 mmoles), acetato de paladio (II) (0.01 g, 0.07 mmoles), y KOAc (0.64 g, 6.6 mmoles) en DMD (7.5 ml) se desgasificó con argón durante 2 minutos a ta. La mezcla luego se calentó a 80°C durante 4 h. Después de enfriar la mezcla a ta, N-(4-bromo-2-fluorofenil)-6-fluoro-1,3-benzotiazol-2-amina (0.74 g, 2.2 mmoles), tetraquis(trifenilfosfina)paladio (0) (0.08 g, 0.07 mmoles) y se agregó $NaHCO_3$ acuoso saturado (5 ml). La mezcla se calentó a 85°C durante la noche. La mezcla se vertió enfriada en hielo y se extrajo con EtOAc. Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se concentró a vacío y se purificó por cromatografía en columna (20% EtOAc en hexanos). Esto dio 0.345 g (39%) del compuesto del título. CL/EM m/z 411.3 (MH^+); tiempo de retención de 4.15 min. RMN ^1H (400 MHz,

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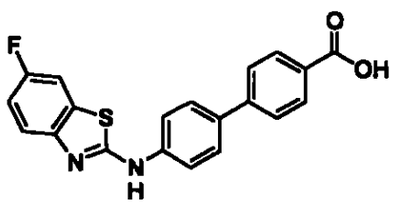
CD_2Cl_2) δ 2.62 (s, 3H), 3.90 (s, 3H), 7.10 (t, 1H), 7.39-7.53 (m, 5H), 7.62-7.70 (m, 1H), 7.99 (d, 1H), 8.58 (t, 1H).

Paso 2. Preparación de ácido 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-carboxílico

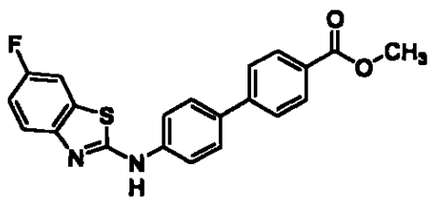


Como se muestra en el Esquema de Reacción 6, se suspendió 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-carboxilato de metilo (0.38 g, 0.67 mmoles) en THF (5 ml), MeOH (5 ml) y agua (2.5 ml), y se agregó NaOH (0.27 g, 6.7 mmoles). La mezcla de reacción se calentó a 50°C durante 3 h. Al enfriarse a ta, la mezcla de reacción se concentró a vacío, se acidificó con HCl 2N, y el sólido resultante se recopiló por filtración. Esto dio 0.33 g (cuantitativo) del compuesto del título. RMN ^1H (400 MHz, DMSO-d_6) δ 2.62 (s, 3H), 7.10 (t, 1H), 7.49-7.58 (m, 5H), 7.65-7.75 (m, 1H), 8.10 (d, 1H), 8.58 (t, 1H), 10.85 (br, 1H).

Intermediario VI-3: ácido 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxílico



Paso 1. Preparación de 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxilato de metilo

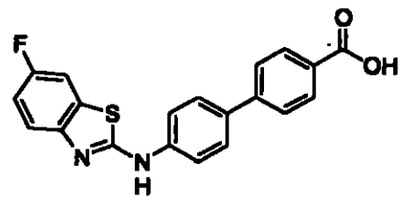


Una mezcla de bis(pinacolato)diboro (0.35 g, 1.4 mmoles), 4-bromobenzoato de metilo (0.30 g, 1.4 mmoles), acetato de paladio (II) (0.01 g, 0.04 mmoles), y KOAc (0.41 g, 4.2 mmoles) en DMF (7.5 ml) se desgasificó con argón durante 30 min a ta. La mezcla se calentó luego a 80°C durante 4 h. Después de que se enfrió la mezcla a ta, N-(4-bromofenil)-6-fluoro-1,3-benzotiazol-2-amina (0.45 g, 1.4

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mmoles), tetraquis(trifenilfosfina)paladio (0) y se agregó (0.05 g, 0.04 mmoles) y $NaHCO_3$ acuoso saturado (5 ml). La mezcla se calentó a 85°C Durante la noche. Al enfriarse a ta, la mezcla se diluyó con EtOAc. Las fases orgánicas combinadas se separaron se secaron sobre Na_2SO_4, y se concentró a vacío. La purificación por cromatografía en columna (25% EtOAc en hexanos) produciendo 0.094 g (18%) del compuesto del titulo. CL/EM m/z 379.3 (MH^+); tiempo de retención 3.87 min. RMN ^1H (400 MHz, CD_3OD) δ 3.93 (s, 3H), 7.95 (t, 1H), 7.39-7.81 (m, 8H), 8.03 (d, 2H).

Paso 2. Preparación de ácido 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxílico

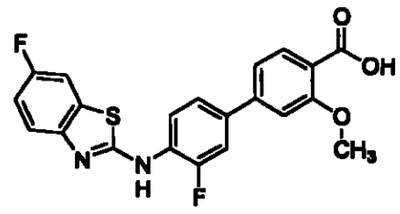


Se suspendió 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxilato de metilo (94 mg, 0.25 mmoles) en THF (3 ml) y agua (1.5 ml) y se agregaron NaOH (0.10 g, 2.5 mmoles). La mezcla de reacción se calentó a 50°C durante 3 h. Al enfriarse a ta, la mezcla de reacción se concentró a

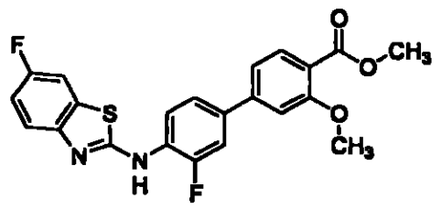
186

vacío, se acidificó con HCl 2N, y el sólido resultante se recopiló por filtración. Esto dio 90 mg (99%) del compuesto del título. CL/EM m/z 365.2 (MH^+), tiempo de retención 3.46 min. RMN ^1H (400 MHz, DMSO-d_6) δ 7.08 (t, 1H), 7.49-7.80 (m, 6H), 7.82-8.01 (m, 4H), 10.75 (br, 1H).

Intermediario VI-4: ácido 4-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxi bifenil-4-carboxílico



Paso 1. Preparación de 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxi-bifenil-4-carboxilato de metilo

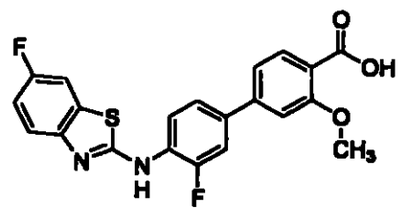


Se desgasificó una mezcla de bis(pinacolato)diboro (1.40 g, 5.51 mmoles), 4-bromo-2-metoxibenzoato de metilo (1.35 g, 5.51 mmoles), acetato de paladio (II) (00.004 g,

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0.17 mmoles) y KOAc (1.62 g, 16.5 mmoles) en DMF (10 ml) con argón durante 30 min a ta. La mezcla luego se calentó a 80°C durante 4 h. Después la mezcla se enfrió a ta, se agregaron N-(4-bromo-2-fluorofenil)-6-fluoro-1,3-benzotiazol-2-amina (1.88 g, 5.51 mmoles), tetraquis(trifenilfosfina)paladio (I) (0.19 g, 0.17 mmoles) y $NaHCO_3$ acuoso saturado (5 ml). La mezcla se calentó a 85°C durante la noche. La mezcla se vertió enfriada en hielo y se extrajo con EtOAc. Las fases orgánicas combinadas se secaron sobre $MgSO_4$, se concentró a vacío, y se purificó por cromatografía en columna (25% EtOAc en hexanos). Esto dio 0.431 g (18%) del compuesto del título CL/EM m/z 427.3 (MH'), tiempo de retención 3.82 min. RMN ^1H (400 MHz, CD_2Cl_2) δ 3.81 (s, 3H), 4.03 (s, 3H), 7.19-7.23 (m, 3H), 7.41-7.64 (m, 4H), 7.82 (d, 1H), 8.31 (t, 1H).

Paso 2. Preparación de ácido 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxi-bifenil-4-carboxílico

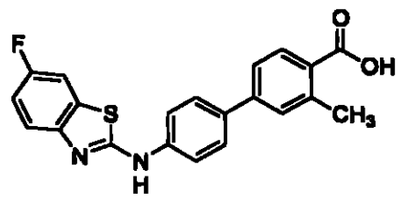


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Se suspendió una mezcla de 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-carboxilato de metilo (0.43 g, 1.01 mmoles) en THF (10 ml), MeOH (5 ml) y agua (5 ml), y se agregó NaOH (0.40 g, 10 mmoles). La mezcla de reacción se agitó a ta durante 18 h. La mezcla de reacción se concentró bajo presión reducida, se acidificó con HCl 2N, y el sólido resultante se recopiló por filtración. Esto dio 0.41 g (99%) del compuesto del título como un sólido café claro. CL/EM m/z (MH^+), tiempo de retención 3.44 min. RMN ^1H (400 MHz, DMSO-d_6) δ 3.91 (s, 3H), 7.17 (t, 1H), 7.24-7.27 (m, 2H), 7.58-7.78 (m, 5H), 8.63 (t, 1H), 10.45 (br, 1H).

Preparación de Compuestos Intermediarios de la Fórmula (VI) por el Método B

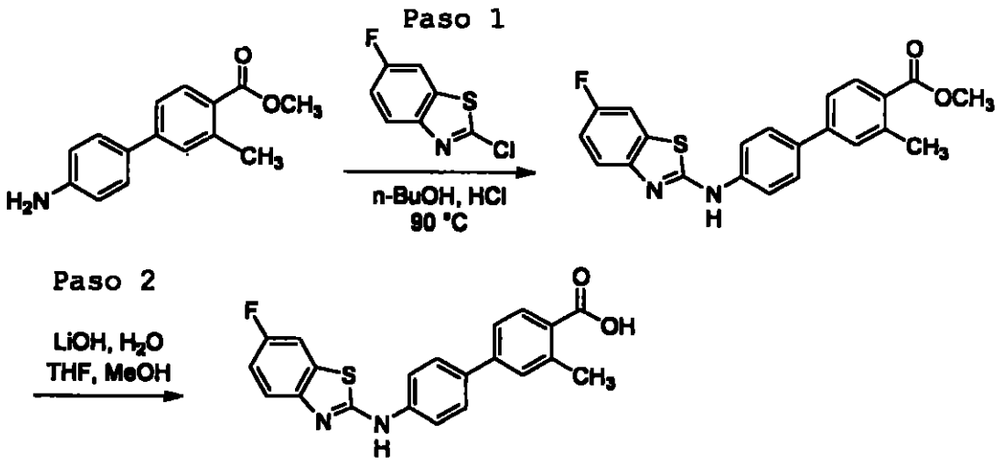
Intermediario VI-5: ácido 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-carboxílico



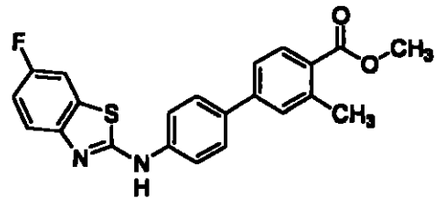
La preparación de ácido 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metildifenil-4-carboxílico se describió más adelante en el Esquema de Reacción 7.

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Esquema de Reacción 7



Paso 1. Preparación de 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-carboxilato de metilo

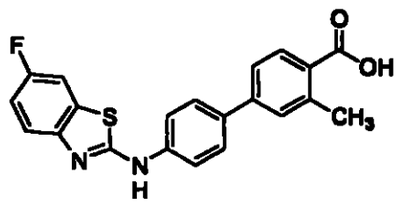


Como se muestra en el Esquema de Reacción 7, una mezcla de 4'-amino-3-metilbifenil-4-carboxilato de metilo (0.34 g, 1.40 mmoles) y 2-cloro-6-fluoro-1,3-benzotiazol (0.26 g, 1.40 mmoles) en n-butanol (4 ml) se calentó a 60-70°C, y luego HCl 4N en 1,4-dioaxano (0.16 ml, 0.63 mmoles) se agregó por goteo con agitación. La mezcla de reacción se

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calentó a 90°C durante 18 h. Al enfriarse a ta, la mezcla de reacción se concentró a vacío. El residuo se trituró con etanol y se recopiló por filtración, dando 0.32 g (58%) del compuesto del título como un sólido amarillo pálido. CL/EM m/z 393.3 (MH^+), tiempo de retención 4.02 min. RMN ^1H (400 MHz, CD_2Cl_2) δ 2.62 (s, 3H), 3.95 (s, 3H), 7.05 (t, 1H), 7.39-7.60 (m, 4H), 7-65 (s, 4H), 7.96 (d, 1H).

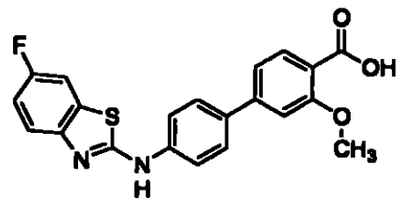
Paso 2. Preparación de ácido 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-carboxílico



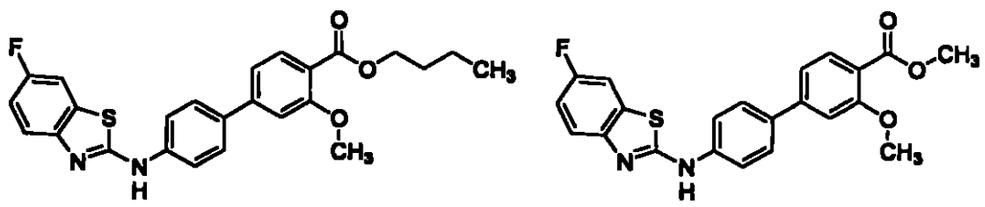
Como se muestra en el Esquema de Reacción 7, se suspendió 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-carboxilato de metilo (0.25 g, 0.65 mmoles) en THF (5 ml), MeOH (5 ml) y agua (2.5 ml) y se agregó NaOH (0.26 g, 6.5 mmoles). La mezcla de reacción se calentó a 50°C durante 3 h. Al enfriarse a TA, la mezcla de reacción se concentró a vacío, se acidificó con HCl 2N, y el sólido resultante se recuperó por filtración. Esto dio 0.25 g (cuantitativo) del compuesto del título. RMN ^1H (400 MHz,

DMSO-d_6) δ 2.62 (s, 3H), 7.05 (t, 1H), 7.57-7.90 (m, 9H), 10.62 (br, 1H).

Intermediario VI-6: ácido 4'-[(6-difluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-carboxílico



Paso 1. Preparación de 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-carboxilato de butilo y 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-carboxilato de metilo

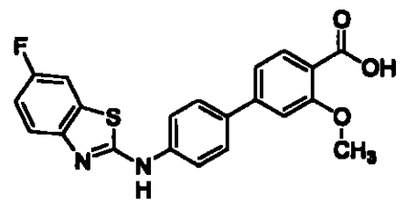


Una mezcla de 4'-amino-3-metoxibifenil-4-carboxilato de metilo (0.27 g, 1.06 mmoles) y 2-cloro-6-fluoro-1,3-benzotiazol (0.20 g, 1.06 mmoles) en n-butanol (8

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ml) se calentó a 60-70°C, y luego HCl 4N en 1,4-dioxano (0.12 ml, 0.48 mmoles) se agregó por goteo con agitación. La mezcla de reacción se calentó a 90°C durante 18 h. Al enfriarse a ta, la mezcla de reacción se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna (25% EtOAc en hexanos), dando 0.209 g (44%) de 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-carboxilato de butilo, y 0.132 g (30%) de 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-carboxilato de metilo [CL/EM m/z 409.3 (MH^+), tiempo de retención = 3.67 min, m/z 451.3 (MH^+), tiempo de retención = 4.25 min. RMN ^1H (400 MHz, CCD_2Cl_2) δ 3.85 (s, 3H), 4.00 (s, 3H), 7.05-726 (m, 3H), 7.42 (d, 1H), 7.61-7.64 (m, 1H), 7.76 (s, 4H), 7.90 (d, 1H)].

Paso 2. Preparación de ácido 4'-[(fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-carboxílico

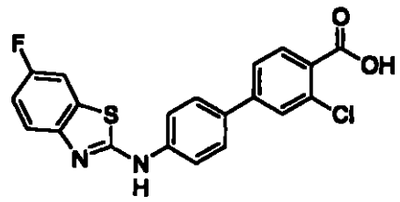


4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-carboxilato de butilo (0.30 g, 0.43 mmoles) y 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-

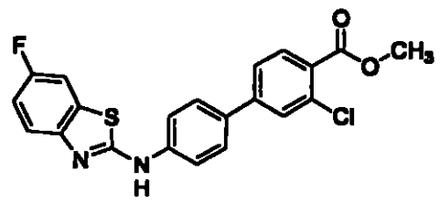
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carboxilato de metilo (0.13 g, 0.25 mmoles) se combinaron en THF (6 ml), MeOH (6 ml) y agua (3 ml) y luego se agregó NaOH (0.09 g, 2.1 mmoles). La mezcla de reacción se calentó a 50°C durante 3 h. Al enfriar a ta, la mezcla de reacción se concentró bajo presión reducida, se acidificó y el sólido resultante se recuperó por filtración. Esto dio 0.286 g (87%) del compuesto del título. CL/EM m/z 395.2 (MH^+), tiempo de retención 3.30 min. RMN ^1H (400 MHz, DMSO-d_6) δ 3.90 (s, 3H), 7.12-7.33 (m, 3H), 7.61-7.90 (m, 7H), 10.62 (br, 1H).

Intermediario VI-7: ácido 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-clorobifenil-4-carboxílico

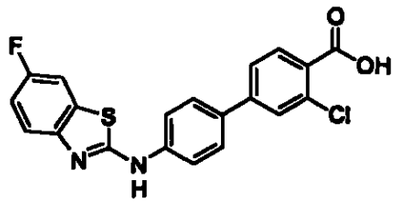


Paso 1. Preparación de 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-clorobifenil-4-carboxilato de metilo



Una mezcla de 4'-amino-3-clorobifenil-4-carboxilato de metilo (0.45 g, 1.7 mmoles) y 2-cloro-6-fluoro-1,3-benzotiazol (0.32 g, 1.7 mmoles) en n-butanol (8 ml) se calentó a 60-70°C, y luego HCl 4N en 1,4-dioxano (0.19 ml, 0.77 mmoles) se agregó por goteo con agitación. La mezcla de reacción se calentó a 90°C durante 18 h. Al enfriar a ta, la mezcla de reacción se concentró bajo presión reducida. El residuo se trituró con etanol, y el sólido se recuperó por filtración. Esto dio 0.399 g (56%) del compuesto del título como un sólido beige. CL/EM m/z 411 (MH^+), tiempo de retención 4.03 min. RMN ^1H (400 MHz, DMSO-d_6) δ 3.85 (s, 3H), 7.12 (t, 1H), 7.67-7.87 (m, 9H), 10.62 (br, 1H).

Paso 2. Preparación de ácido 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-clorobifenil-4-carboxílico

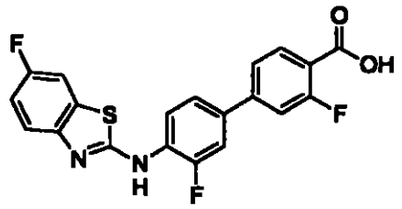


Se suspendió 4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-clorobifenil-4-carboxilato de metilo (0.30 g, 0.71 mmoles) en THF (5 ml), MeOH (5 ml) y agua (2.5 ml) y luego NaOH (0.28 g, 7.1 mmoles). La mezcla de reacción se

calentó a 50°C durante 3 h. Al enfriarse a TA, la mezcla de reacción se concentró bajo presión reducida, se acidificó el sólido resultante se recuperó por filtración. Esto dio 0.34 g (cuantitativo) del compuesto del título. CL/EM m/z 399.2 (MH^+), tiempo de retención 3.53 min.

Preparación de Compuestos Intermediarios de la Fórmula (VI) por el Método A

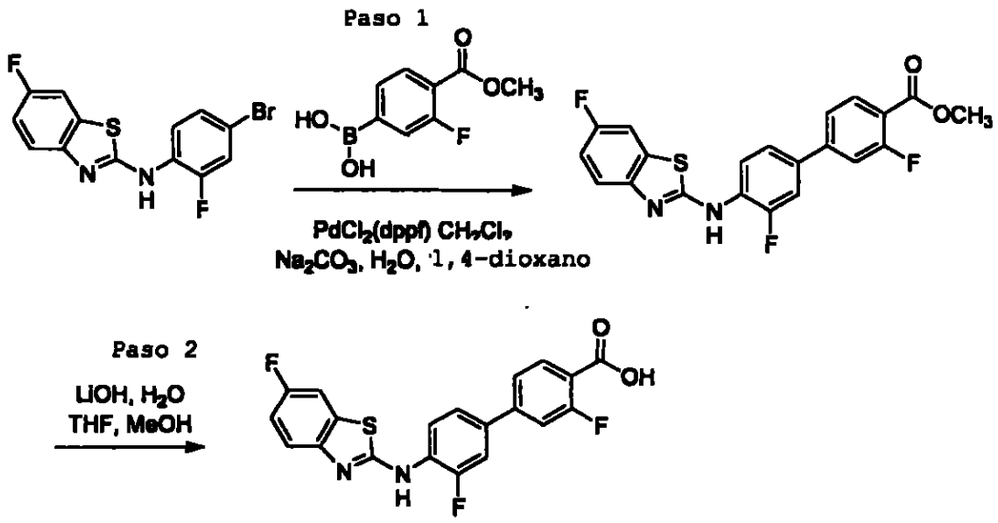
Intermediario VI-8: ácido 3,3'-difluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxílico



La preparación de ácido 3,3'-difluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxílico se describe en seguida del Esquema de Reacción 8.

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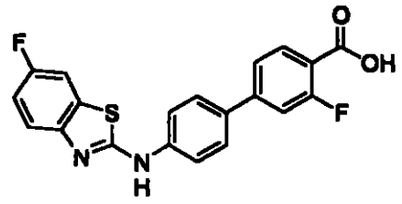
Esquema de Reacción 8



Como se muestra en el Esquema de Reacción 8, el Intermediario VI-8 (ácido 3,3'-difluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxílico) se preparó usando un método similar al empleado en la preparación del Intermediario VI-1 usando N-(4-bromo-2-fluorofenil)-6-fluoro-1,3-benzotiazol-2-amina y ácido [3-fluoro-4-(metoxicarbonil)fenil]borónico comercialmente disponible como materiales de partida.

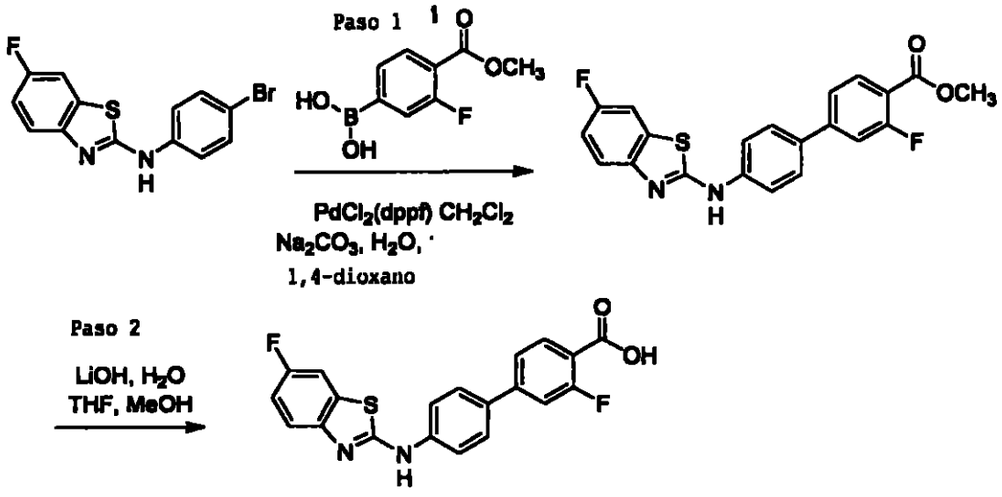
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Intermediario VI-9: ácido 3-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxílico



La preparación de ácido 3-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxílico se describe en seguida en el Esquema de Reacción 9.

Esquema de Reacción 9

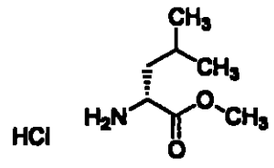


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Como se muestra en el Esquema de Reacción 9, se preparó el Intermediario VI-9 (ácido 3-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil]-4-carboxílico) usando un método similar al empleado en la preparación del Intermediario VI-1 usando N-(4-bromo-2-fluorofenil)-6-fluoro-1,3-benzotiazol-2-amina y ácido [3-fluoro-4-(metoxicarbonil)fenil]borónico comercialmente disponible como materiales de partida.

Preparación de Compuestos de la Fórmula (VII)

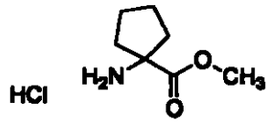
Intermediario VIII-1: Clorhidrato de D-leucinato de metilo



Se agregó D-leucina (3.00 g, 22.9 mmoles) a una solución de cloruro de acetilo (1.70 ml, 23.9 mmoles) en metanol (30 ml). La mezcla de reacción se dejó agitar durante 18 h y luego se concentró bajo presión reducida. Esto dio 3.8 g (91%) del compuesto del título. RMN ^1H (400 MHz, CD_3OD) δ 0.99 (dd, 6H), 1.63-1.87 (m, 3H), 4.10 (dd, 1H), 3.81 (s, 3H).

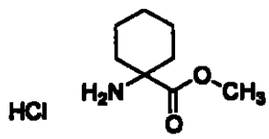
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Intermediario VIII-2: Clorohidrato de 1-aminociclopentancarboxilato de metilo



Se agregó ácido 1-aminociclopentancarboxílico (1.00 g, 7.74 mmoles) a una solución de cloruro de acetilo (0.60 ml, 8.44 mmoles) en metanol (10 ml). La mezcla de reacción se dejó agitar durante 18 hr bajo presión reducida. Esto dio 1.35 g (97% del compuesto del título. RMN ^1H (400 MHz, CD_3OD) δ 1.80-2.00 (m, 6H), 2.34-2.39 (m, 2H), 3.82 (s, 3H).

Intermediario VIII-3: Clorhidrato de 1-aminociclohexancarboxilato de metilo

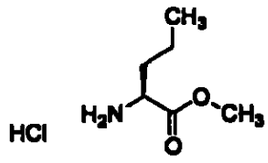


Acido 1-aminociclohexancarboxílico 1.00 g, 6.98 moles) se agregó a una solución de cloruro de acetilo (0.60 ml, 8.44 mmoles) en metanol (10 ml). La mezcla de reacción se dejó agitar durante 18 horas y luego se concentró bajo

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presión reducida. RMN ^1H (400 MHz, CD_3OD) δ 1.42-1.82 (m, 8H), 2.08-2.20 (m, 2H), 3.82 (s, 3H).

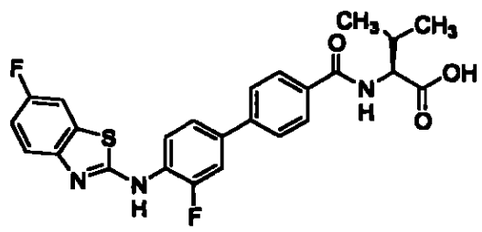
Intermediario VIII-4: Clorohidrato de L-norvalinato de metilo



Se agregó L-Norvalina (0.82 g, 6.98 mmoles) a una solución de cloruro de acetilo (0.60 ml, 8.44 mmoles) en metanol (10 ml). La mezcla de reacción se dejó agitar durante 18 h y luego se concentró bajo presión reducida. RMN ^1H (400 MHz, CD_3OD) δ 1.0 (t, 3H), 1.35-1.50 (m, 2H), 1.80-2.00 (m, 2H), 3.82 (s, 3H).

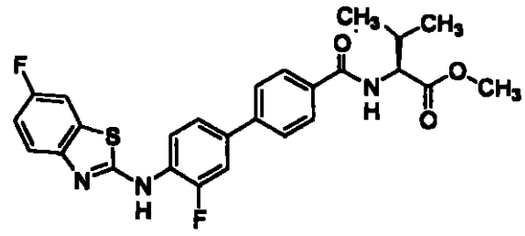
Preparación de Compuestos de la Fórmula (I)

Ejemplo I: N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino[bifenil-4-il]carbonil)-L-valina



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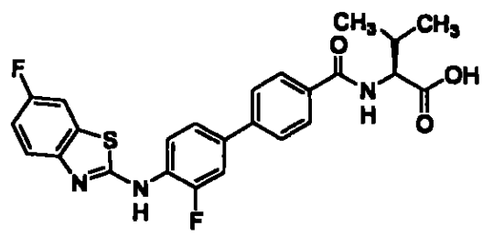
Paso 1. Preparación de N-[3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il]carbonil)-L-valinato de metilo



El ácido 3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-carboxílico (0.084 g, 0.22 mmoles) y el clorhidrato de éster L-valina metílico (0.044 g, 0.26 mmoles) se suspendieron en CH_2Cl_2 (5 ml), y trietilamina (0.04 ml, 0.26 mmoles), 1-hidroxibenzotriazol (0.0296 g, 0.22 mmoles) y se agregaron N-N'-diisopropilcarbodiimida (0.030 ml, 0.22 mmoles). Se agregó DMF (2.0 ml) para lograr disolución y la mezcla de reacción se agitó a ta durante la noche. La mezcla de reacción se diluyó con EtOAc (50 ml) y se lavó con agua (2 x 50 ml) y salmuera (50 ml). Las fases orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y concentraron a vacío. El material crudo se purificó por cromatografía en columna instantánea (sistema Biotage®; gradiente de 30-40% EtOAc/Hexanos). Esto dio 90.4 mg (83%) del producto deseado como un sólido blanco.

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Paso 2. Preparación de N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina

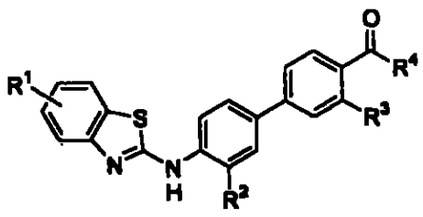


N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valinato (84.2 mg, 0.17 mmoles) se suspendió en THF (2.6 ml), MeOH (2.5 ml) y agua (1 ml), y se agregó LiOH (40.7 mg, 1.70 mmoles). La mezcla de reacción se calentó a 50°C durante 2 h. Al enfriar a ta, la mezcla de reacción se llevó a pH 3 con HCl 1N y se extrajo con EtOAc (3x 25 ml). Las fases orgánicas combinadas se lavaron con agua (2 x 50 ml) y salmuera (50 ml), se secó sobre $MgSO_4$, se filtró y se concentró a vacío. Esto dio 72.3 mg (88%) del compuesto del título como un sólido blanco. CL/EM m/z 482.3 (MH^+), tiempo de retención 3.46 min. RMN ^1H (400 MHz, DMSO-d_6) δ 0.99 (dd, 6H), 2.19-2.24 (m, 1H), 4.30 (dd, 1H), 7.60-7.84 (m, 6H), 7.88 (d, 2H), 8.42 (d, 1H), 8.66 (t, 1H), 10.42 (s, 1H).

Usando los métodos descritos antes y sustituyendo los materiales de partida apropiados, se prepararon de manera

similar los compuestos de la Fórmula (I), listados en la Siguiente Tabla 1.

Tabla 1a. Ejemplos Preparativos de los Compuestos de la Fórmula (I)



Ejemplo No.	R^1	R^2	R^3	R^4	CL-EM Tpo. Ret. (min)	CL-EM $[M+H]^+$	Método
1	6-F	F	H	L-Val-OH	3.46	482.3	A
2	6-F	H	H	L-Ala-OH	3.50	436.3	A
3	6-F	F	H	L-Ala-OH	3.55	454.3	A
4	6-F	H	H	L-Val-OH	3.72	464.3	A
5	6-F	H	Cl	L-Val-OH	3.46	498.2	B
6	6-F	F	CH_3	L-Val-OH	3.47	496.2	A
7	6-F	F	OMe	L-Val-OH	3.60	512.4	A
8	6-F	H	H	L-Leu-OH	3.86	478.3	A
9	6-F	F	H	L-Leu-OH	3.93	496.3	A
10	6-F	H	OMe	L-Leu-OH	3.64	508.2	B
11	6-F	F	OMe	L-Leu-OH	3.75	526.4	A
12	6-F	H	Cl	L-Leu-OH	3.62	512.2	B

Ejemplo No.	R^1	R^2	R^3	R^4	CL-EM Tpo. Ret. (min)	CL-EM $[M+H]^+$	Método
13	6-F	H	CH_3	L-Leu-OH	3.55	492.2	B
14	6-F	F	CH_3	L-Leu-OH	3.60	510.4	A
15	6-F	H	H	D-Leu-OH	3.48	478.2	A
16	6-F	F	H	D-Leu-OH	3.58	496.2	A
17	6-F	H	H	L-Ile-OH	3.52	478.2	A
18	6-F	F	H	L-Ile-OH	3.64	496.4	A
19	6-F	F	OMe	L-Ile-OH	3.75	526.4	A
20	6-F	H	H	L-Phe-OH	3.85	512.3	A
21	6-F	F	H	L-Phe-OH	3.93	530.2	A
22	6-F	H	OMe	L-Phe-OH	3.63	508.2	B
23	6-F	H	CH_3	L-Phe-OH	3.51	526.2	A
24	6-F	F	CH_3	L-Phe-OH	3.61	544.3	A
25	6-F	H	Cl	L-Phe-OH	3.60	546.1	B
26	6-F	H	H	L-Pro-OH	3.52	462.2	A
27	6-F	F	H	L-Pro-OH	3.58	480.2	A
28	6-F	H	OMe	L-Pro-OH	3.20	492.1	B
29	6-F	H	Cl	L-Pro-OH	3.32	496.1	B
30	6-F	H	CH_3	L-Pro-OH	3.52	476.1	B
31	6-F	F	CH_3	L-Pro-OH	3.31	494.3	A

Tabla 1b. Nombres de la IUPAC para Compuestos en la Tabla 1a

Ejemplo No.	Nombre IUPAC
1	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-valina
2	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L- alanina
3	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina
4	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina

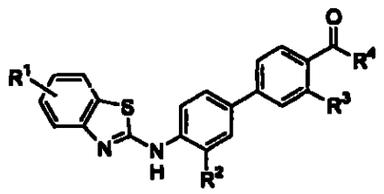
Ejemplo No.	Nombre IUPAC
5	N-({3-cloro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il} carbonil)-L-valina
6	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il} carbonil)-L-valina
7	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il]carbonil)-L-valina
8	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-leucina
9	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-leucina
10	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-leucina
11	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-leucina
12	N-({3-cloro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-leucina
13	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-leucina
14	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-leucina
15	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-D- leucina
16	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-D-leucina
17	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-isoleucina
18	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-isoleucina
19	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-isoleucina
20	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L- fenilalanina
21	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-fenilalanina
22	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-fenilalanina
23	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-fenilalanina
24	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-fenilalanina

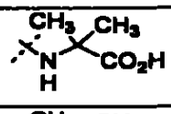
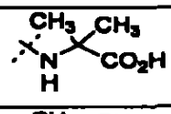
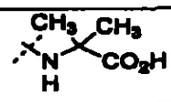
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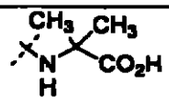
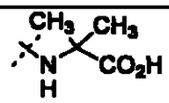
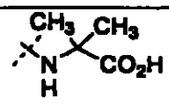
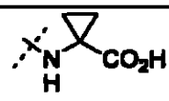
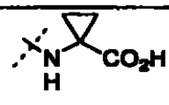
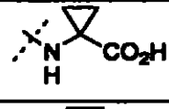
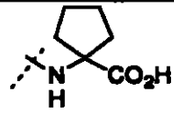
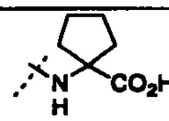
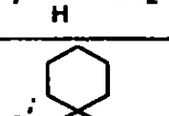
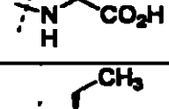
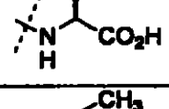
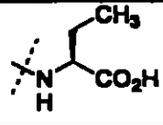
Ejemplo No.	Nombre IUPAC
25	N-({3-cloro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-fenilalanina
26	1-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-prolina
27	1-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-prolina
28	1-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4- il}carbonil)-L-prolina
29	1-({3-cloro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-prolina
30	1-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-prolina
31	1-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-prolina

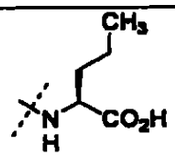
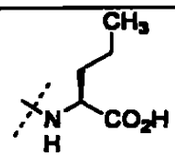
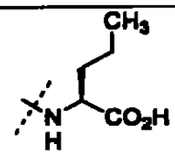
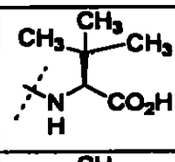
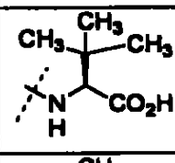
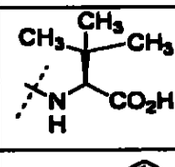
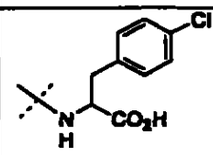
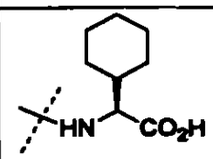
Usando los métodos descritos antes y sustituyendo los materiales de partida apropiados, se prepararon de manera similar los compuestos de la Fórmula (I), listados en la siguiente Tabla 2a.

Tabla 2a. Ejemplos Preparativos de los Compuestos de la Fórmula (I)



Ejemplo No.	R^1	R^2	R^3	R^4	CL-EM Tpo. Ret. (min)	CL-EM [M+H]$^+$ (m/z)	Método
32	6-F	H	H		3.57	450.2	A
33	6-F	F	H		3.64	468.2	A
34	6-F	H	OCH_3		3.35	480.1	B

Ejemplo No.	R^1	R^2	R^3	R^4	CL-MS Tpo. Ret. (min)	CL-EM $[M+H]^+$	Método
35	6-F	H	Cl		3.30	484.1	B
36	6-F	H	CH_3		3.24	464.2	B
37	6-F	F	CH_3		3.28	482.3	A
38	6-F	H	H		3.48	448.2	A
39	6-F	F	H		3.23	466.3	A
40	6-F	F	OCH_3		3.34	496.3	A
41	6-F	H	H		3.74	476.3	A
42	6-F	F	H		3.49	494.3	A
43	6-F	H	H		3.87	490.3	A
44	6-F	H	H		3.25	450.1	A
45	6-F	F	H		3.37	468.3	A
46	6-F	F	OCH_3		3.50	498.4	A

Ejemplo No.	R^1	R^2	R^3	R^4	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
47	6-F	H	H		3.76	464.3	A
48	6-F	F	H		3.55	482.4	A
49	6-F	F	OCH_3		3.63	512.3	A
50	6-F	H	H		3.52	478.2	A
51	6-F	F	H		3.63	496.3	A
52	6-F	F	OCH_3		3.73	526.4	A
53	6-F	H	H		3.68	546.1	A
54	6-F	H	H		3.68	504.2	A

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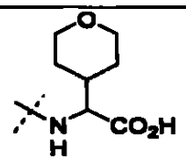
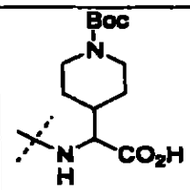
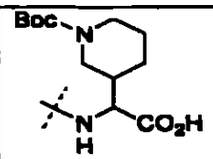
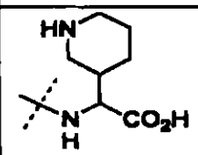
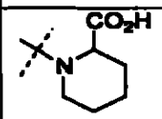
Ejemplo No.	R^1	R^2	R^3	R^4	CL-EM Tpo. Ret. (min)	CL-EM $[M+H]^+$	Método
55	6-F	H	H		3.15	506.2	A
56	6-F	H	H		3.60	605.0	A
57	6-F	H	H		3.65	605.1	A
58	6-F	H	H		2.98	505.2	A
59	6-F	F	H		3.80	494.2	A

Tabla 2b. Nombres IUPAC para Compuestos en Tabla 2a

Ejemplo No.	Nombre de IUPAC
32	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-2-metilalanina
33	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-2-metilalanina
34	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4- il}carbonil)-2-metilalanina
35	N-({3-cloro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-2-metilalanina
36	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4- il}carbonil)-2-metilalanina

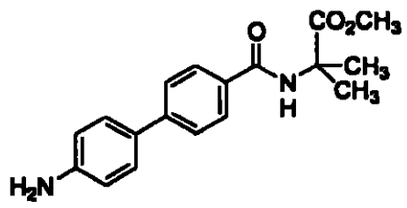
Ej. No.	Nombre IUPAC
37	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il) amino]-3-metilbifenil-4-il}carbonil)-2-metilalanina
38	Acido 1-[({4'-[(6-fluoro-1,3-benzotiazol-2-il) amino]bifenil-4-il}carbonil)amino]ciclo propanocarboxilico
39	Acido 1-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il) amino]bifenil-4- il}carbonil)amino]ciclopropanocarboxilico
40	Acido 1-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)amino]ciclopropanocarboxilico
41	Acido 1-[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil,amino]ciclopentanocarboxilico
42	Acido 1-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]ciclopentanocarboxilico
43	Acido 1-[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]ciclohexanocarboxilico
44	Acido (2S)-2-[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)amino]butanoico
45	Acido (2S)-2-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)amino]butanoico
46	Acido (2S)-2-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3- metoxibifenil-4-il}carbonil)amino]butanoico
47	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L- norvalina
48	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-norvalina
49	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il)carbonil)-L-norvalina
50	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il)carbonil'-3- metil-L-valina
51	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-3-metil-L-valina
52	N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-3-metil-L-valina
53	4-cloro-N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)fenilalanina
54	Acido(2S)-ciclohexil[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)amino]acético
55	Acido [({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino](tetrahidro-2H-piran-4-il)acético
56	Acido [1-(tert-butoxicarbonil)piperidin-4-il][({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]acético

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Ejemplo No.	Nombre de IUPAC
57	Acido [1-(tert-butoxicarbonil)piperidin-3-il][({4'-[(6-fluoro-1,3-benzotiazol-2- il)amino]bifenil-4-il}carbonil)amino]acético
58	Acido [({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino] bifenil-4- il}carbonil)amino](piperidin-3-il)acético
59	Acido 1-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)piperidina-2-carboxílico

Preparación de Compuestos Intermediarios de la Fórmula (XIII) por el Método C

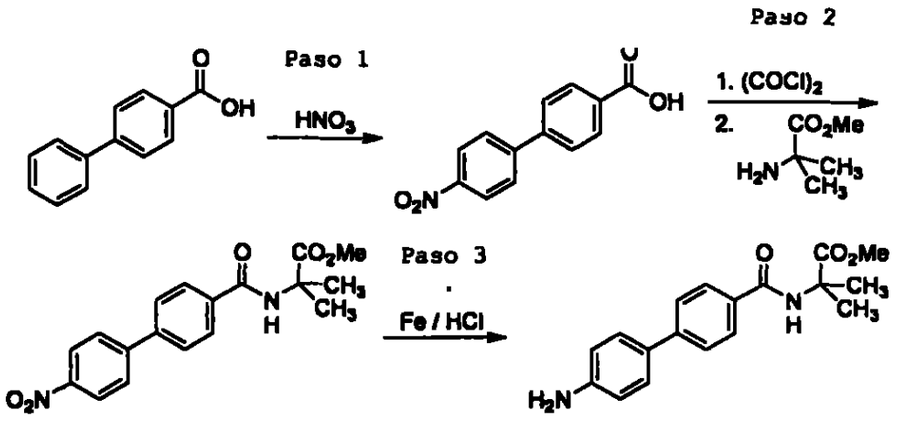
Intermediario XIII-1: N-[(4'-aminobifenil-4-il)carbonil]-2-metilalaninato de metilo



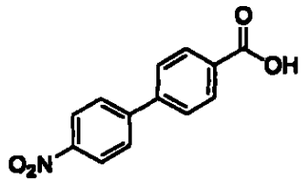
La preparación de N-[(4'-aminobifenil-4-il)carbonil]-2-metilalaninato se describió más adelante en el Esquema de Reacción 10.

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Esquema de Reacción 10



Paso 1. Preparación de ácido 4'-nitro-1,1'-bifenil-4-carboxílico

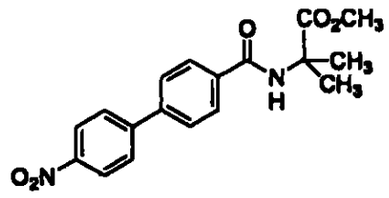


Como se muestra en el Esquema de Reacción 10, se le agregó al ácido nítrico enfriado en hielo ácido 4-bifenilcarboxílico (9.4 g, 20.0 mmoles), y la mezcla resultante se agitó con enfriamiento en un baño de agua de hielo durante 1h. La mezcla se vertió en agua de hielo y se filtró. El sólido recuperado se suspendió en etanol y se calentó a reflujo durante 2 h. La mezcla se filtró en

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caliente, se lavó con etanol y se secó bajo alto vacío para dar ácido 4-nitro-1,1'-bifenil-4-carboxílico (2.3 g, 47%). RMN ^{1}H (400 MHz, DMSO-d_6) δ 7.89 (d, 2H), 8.01 (d, 2H), 8.05 (d, 2H), 8.31 (d, 2H), 13.12 (d, 2H).

Paso 2. Preparación de 2-metil-N-[(4'-nitrobifenil-4-il)carbonil]alaninato de metilo

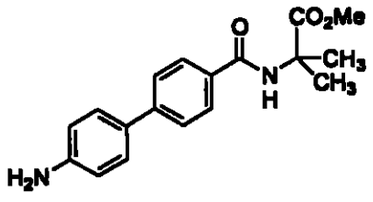


Como se muestra en el Esquema de Reacción, se disolvió ácido 10,4'-nitro-1,1'-bifenil-4-carboxílico (4.66 g, 19.2 mmoles) en cloruro de metileno (110 ml), y luego se añadió cloruro de oxalilo (2.51 ml, 28.7 mmoles), seguido por 3 gotas de N-N-dimetilformamida. La mezcla resultante se agitó a ta durante 45 minutos, se concentró bajo presión reducida y se secó además bajo vacío durante 30 min. El residuo se disolvió en cloruro de metileno (75 ml) y se agregó por goteo a una mezcla de agua de hielo de clorhidrato de 2-metilalaninato de metilo (3.83 g, 24.9 mmoles), cloruro de metileno (75 ml), y trietilamina (6.68 ml, 47.9 moles). La solución resultante se agitó a ta durante 1 h y luego a 55°C durante 2 h. La mezcla se dejó enfriar a ta y luego se lavó

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con solución de HCl acuosa 1N (5 ml) y agua (2 x 20 ml). La capa orgánica se separó, se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó por cromatografía instantánea (sistema Biotage®, hexanos/EtOAc 4:1) para dar 2-metil-N-[(4'-nitrobifenil-4-il)carbonil]alaninato de metilo (6.21 g, 95%). RMN ^1H (400 MHz, $CDCl_3$) δ 1.73 (s, 6H), 3.82 (s, 3H), 6.89 (s amplio, 1 H), 7.69 (d, 2H), 7.77 (d, 2H), 7.92 (d, 2H), 8.31 (d, 2H); CL-EM m/z 342.9 (MH^+), tiempo de retención 2.98 minutos.

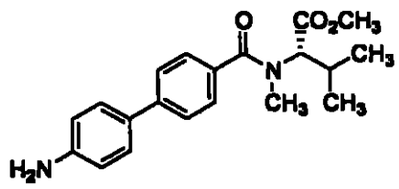
Paso 3. Preparación de N-[(4'-aminobifenil-4-il)carbonil]-2-metilalaninato de metilo



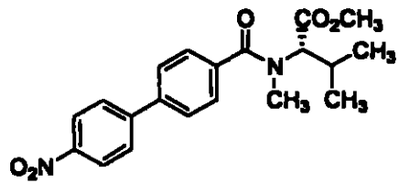
Como se muestra en el Esquema de Reacción 10, a una solución de 2-metil-N-[(4'-nitrobifenil-4-il)carbonil]alaninato de metilo (1.59 g, 4.6 mmoles) en etanol al 85% (50 ml) se le agregó polvo de hierro (2.59 g, 46.4 mmoles) 7 solución de HCl acuoso 2M (2.32 ml, 4.6 mmoles). La mezcla resultante se calentó a reflujo durante 2 h. La mezcla se filtró luego a través de una almohadilla de Celite® y se concentró bajo presión reducida para dar N-[(4'-

aminobifenil-4-il)carbonil]-2-metilalaninato como un sólido amarillo (2.48 g, 99%). RMN ^{1}H (400 MHz, DMSO-d_6) δ 1.44 (s, 6H), 3.57 (s, 3H), 5.33 (s amplio, 2H), 6.61 (d, 2H), 7.41 (d, 2H), 7.58 (d, 2H), 7.83 (d, 2H), 8.54 (s amplio, 1H); CL-EM m/z 313.2 (MH^+), tiempo de retención 1.54 minutos.

Intermediario XIII-2: N-[(4'-aminobifenil-4-il)carbonil]-N-metil-L-valinato de metilo



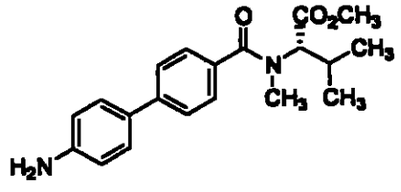
Paso 1. Preparación de N-metil-N-[(4'-nitro-1,1'-bifenil-4-il)carbonil]-L-valinato de metilo



Se disolvió ácido 4'-nitro-1,1'-bifenil-4-carboxílico (0.50 g, 2.0 mmoles) en cloruro de metileno (25 ml) y luego se agregó cloruro de oxalilo (0.27 ml, 3.1 mmoles), seguido por una gota de N,N-dimetilformamida. La mezcla resultante se calentó a 50°C durante 1 h, se concentró

bajo presión reducida y además se secó bajo vacío durante 30 min. El residuo se disolvió en cloruro de metileno (20 ml) y se agregó por goteo a una mezcla de agua de hielo de clorhidrato N-metil-L-valinato de metilo (0.48 g, 2.6 mmoles), cloruro de metileno (50 ml) y trietilamina (1.44 ml, 10.2 mmoles). La solución resultante se agitó enhielo durante 1 h y luego a ta durante la noche. La mezcla se diluyó con cloruro de metileno y se lavó con Solución de HCl acuosa 1N y salmuera. La capa orgánica se separó y se concentró bajo presión reducida. El residuo se purificó por cromatografía instantánea (sistema Biotage®, hexanos/EtOAc 3:1) para dar N-metil-N-[(4'-nitro-1,1'-bifenil-4-il)carbonil]-L-valinato de metilo (0.70 g, 92%). RMN ^1H (400 MHz, $CDCl_3$) δ 0.85 (dd, 3H), 1.06 (dd, 3H), 2.31 (m, 1H), 3.02 (d, 3H), 3.77 (d, 3H), 3.94 (d, 0.5 H), 4.98 (d, 0.5 H), 7.52 (m, 2H), 7.64 (m, 2H), 7.72 (t, 2H), 8.27 (d, 2H); CL-EM m/z 371.2 (MH^+), tiempo de retención 3.27 minutos.

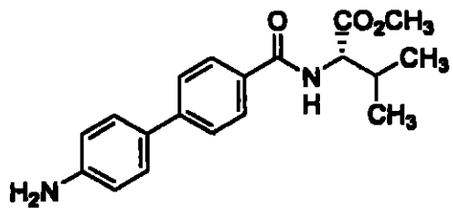
Paso 2. Preparación de N-[(4'-amino-1,1'-bifenil-4-il)carbonil]-N-metil-L-valinato de metilo



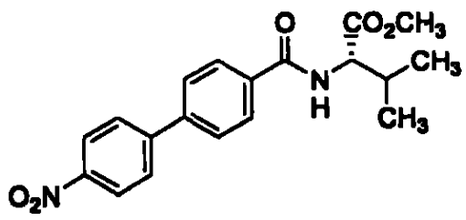
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A una solución de N-metil-N-[(4'-nitro-1,1'-bifenil-4-il)carbonil]-L-valinato de metilo (0.70 g, 1.9 mmoles) en etanol al 85% (20 ml) se le agregó polvo de hierro (1.05 g, 18.9 mmoles) y solución de HCl acuosa 2N (0.41 ml). La mezcla resultante se calentó a reflujo durante 2 h. La mezcla luego se filtró a través de una almohadilla de Celite® y se concentró bajo presión reducida. El residuo se disolvió en cloruro de metileno, se lavó con agua y salmuera, se secó (Na_2SO_4) y se concentró bajo presión reducida para dar N-[(4'-amino-1,1'-bifenil-4-il)carbonil]-N-metil-L-valinato de metilo (0.49 g, 76%). RMN ^1H (400 MHz, CD_3OD) δ 0.85 (dd, 3H), 1.06 (dd, 3H), 2.35 (m, 1H), 3.02 (d, 3H), 3.75 (d, 3H), 4.05 (d, 0.5 H), 4.78 (d, 0.5H), 6.78 (d, 2H), 7.42 (m, 4H), 7.63 (d, 2H),; CL-EM m/z 341.3 (MH^+), tiempo de retención 2.37 minutos.

Intermediario XIII-3: N-[(4'-amino-1,1'-bifenil-4-il)carbonil]-L-valinato de metilo



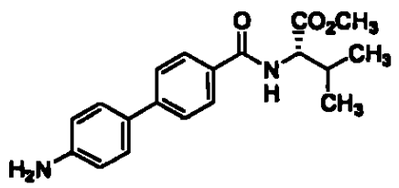
Paso 1. Preparación de Metil-N-[(4'-nitro-1,1'-bifenil-4-il)carbonil]-L-valinato



Se disolvió ácido 4'-nitro-1,1'-bifenil-4-carboxílico (0.60 g, 2.4 mmoles) en cloruro de metileno (25 ml) y luego se agregó cloruro de oxalilo (0.32 ml, 3.7 mmoles), seguido por una gota de N,N-dimetilformamida. La mezcla resultante se calentó a 50°C durante 1h, se concentró bajo presión reducida y además se secó bajo vacío durante 30 min. El residuo se disolvió en cloruro de metileno (20 ml) y se agregó por goteo a una mezcla enfriada en hielo de clorhidrato de L-valinato de metilo (0.54 mg, 3.2 mmoles), cloruro de metileno (20 ml) y trietilamina (1.74 ml, 12.3 mmoles). La solución resultante se agitó en hielo durante 1 h y luego a ta durante la noche. La mezcla se diluyó con cloruro de metileno y se lavó con solución de HCl acuosa 1N y salmuera. La capa orgánica se separó y se concentró bajo presión reducida. El residuo se purificó por cromatografía instantánea (sistema Biotage®, hexanos/EtOAc 2:1) para dar metil-N-[(4'-nitro-1,1'-bifenil-4-il)carbonil]-L-valinato

(0.70 g, 80%). RMN ^1H (400 MHz, CD_3OD) δ 1.06 (dd, 6H), 2.38 (m, 1H), 3.77 (s, 3H), 4.52 (d, 1H), 4.52 (d, 1H), 7.82 (d, 2H), 7.91 (d, 2H), 7.97 (d, 2H), 8.33 (d, 2H); CL-EM m/z 357.1 (MH^+), tiempo de retención 3.07 minutos.

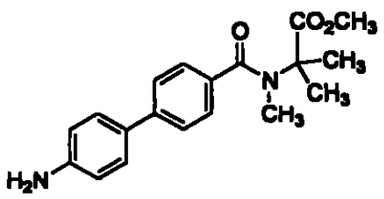
Paso 2. Preparación de N-[(4'-amino-1,1'-bifenil-4-il)carbonil]-L-valinato de metilo



A una solución de metil-N-[(4'-nitro-1,1'-bifenil-4-il)carbonil]-L-valinato (0.70 g, 1.9 mmoles) en etanol al 85% (20 ml) se le agregó polvo de hierro (1.09 g, 19.6 mmoles) y solución de HCl acuosa 2N (1.0 ml). La mezcla resultante se calentó a reflujo durante 2 h. La mezcla luego se filtró a través de una almohadilla de Celite® y se concentró bajo presión reducida. El residuo se disolvió en diclorometano y se lavó con agua y salmuera, se secó (Na_2SO_4), y se concentró bajo presión reducida para dar N-[(4'-amino-1,1'-bifenil-4-il)carbonil]-L-valinato de metilo (0.58 g, 90%). RMN ^1H (400 MHz, CD_3OD) δ 1.03 (dd, 6H), 2.26 (m, 1H), 3.74 (s, 3H), 4.48 (d, 1H), 6.77 (d, 2H), 7.43 (d, 2H), 7.62

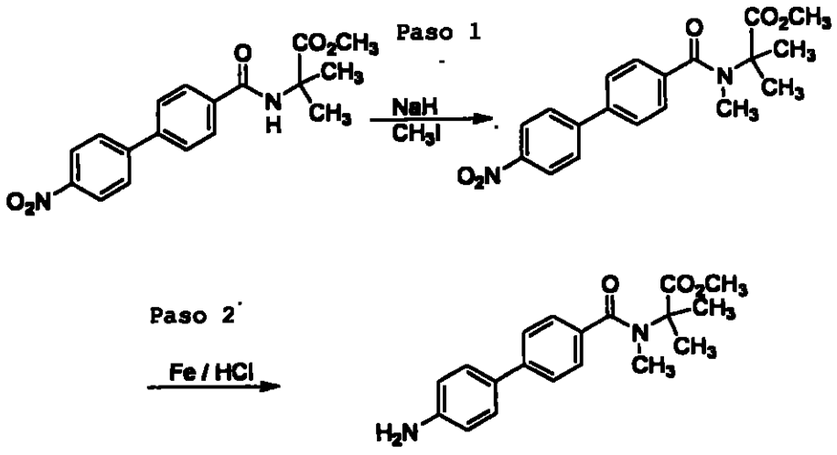
(d, 2H, 7.83 (d, 2H); CL-EM M/z 327.1 (MH^+), tiempo de retención 2.27 minutos.

Intermediario XIII-4: N-[(4'-aminobifenil-4-il)carbonil]-N,2-dimetilalaninato de metilo



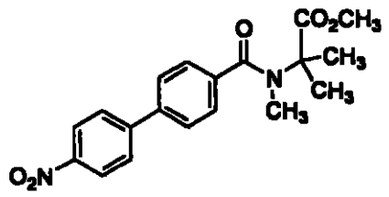
La preparación de N-[(4'-aminobifenil-4-il)carbonil]-N,2-dimetilalaninato de metilo se describe delante del Esquema de Reacción 11.

Esquema de Reacción 11



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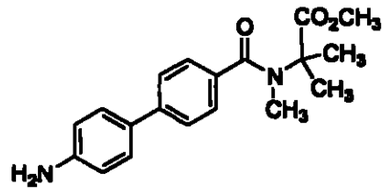
Paso 1. Preparación de N,2-dimetil-N-[(4'-nitrobifenil-4-il)carbonil]alaninato de metilo



Como se muestra en el Esquema de Reacción 11, una mezcla de 2-metil-N-[(4'-nitrobifenil-4-il)carbonil]alaninato de metilo (1.32 g, 3.9 mmoles), hidruro de sodio (117 mg, 4.6 mmoles), y N,N-dimetilformamida (15 ml) se agitó durante 2 h a ta. Se agregó yodometano (0.48 ml, 7.7 mmoles), y la mezcla de reacción se agitó durante la noche a ta. Se agregó agua (30 ml), y la mezcla se extrajo con acetato de etilo (2 x 10 ml). Los extractos combinados se evaporaron a sequedad, y el producto crudo se purificó por cromatografía instantánea (Biotage®, hexanos/EtOAc 4:1) para dar N,2-dimetil-N-[(4'-nitrobifenil-4-il)carbonil]alaninato de metilo como un sólido blanquecino (1.29 g, 94%). RMN ^{1}H (400 MHz, DMSO-d_6) δ 1.47 (s, 6H), 2.93 (s, 3H), 3.58 (s, 3H), 7.52 (d, 2H), 7.84 (d, 2H), 7.98 (d, 2H), 8.30 (d, 2H); CL-EM m/z 356.9 (MH^+), tiempo de retención 2.98 minutos.

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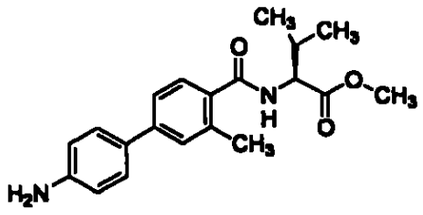
Paso 2. Preparación de N-[(4'-aminobifenil-4-il)carbonil]-N,2-dimetilalaninato de metilo



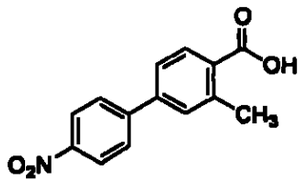
Como se muestra en el Esquema de Reacción 11, a una solución de N,2-dimetil-N-[(4'-nitrobifenil-4-il)carbonil]alaninato de metilo (1.92 g, 5.4 moles) en 85% etanol (50 ml) se le agregó polvo de hierro (3.01 g, 53.88 mmoles) y solución de HCl acuosa 2M (2.69 ml, 5.4 mmoles). La mezcla resultante se calentó a reflujo durante 2.5 h. La mezcla se filtró a través de una almohadilla de Celite® y se concentró bajo presión reducida para dar N-[(4'-aminobifenil-4-il)carbonil]-N,2-dimetilalaninato de metilo como un sólido amarillo (1.44 g, 82%). RMN ^{1}H (400 MHz, DMSO-d_6) δ 1.42 (s, 6H), 2.94 (s, 3H), 3.57 (s, 3H), 5.30 (s amplio, 2H), 6.61 (d, 2H), 7.31-7.40 (m, 4H), 7.58 (d, 2H); CL-EM m/z 327.2 (MH^+), tiempo de retención 1.84 minutos.

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Intermediario XIII-5: N-[(4'-amino-3-metilbifenil-4-il)carbonil]-L-valinato de metilo



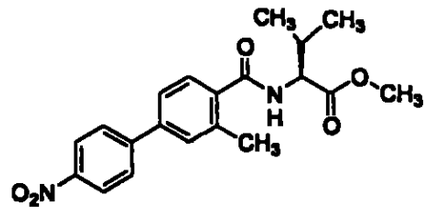
Paso 1. Preparación de ácido 3-metil-4'-nitrobifenil-4-carboxílico



3-metil-4'-nitrobifenil-4-carboxilato De metilo (0.70 g, 2.1 mmoles) se suspendió en THF (5 ml), MeOH (5 ml) y agua (2.5 ml) y se añadió NaOH (0.41 g, 10.3 mmoles). La mezcla de reacción se calentó a 50°C durante 3 h. Al enfriarse a ta, la mezcla de reacción se concentró al vacío y se purificó por CLAR de fase inversa para dar 0.498 g (94%) del compuesto del título. RMN ^{1}H (400 MHz, DMSO-d_6) δ 2.62 (s, 3H), 7.62-7.68 (m 2H), 7.91-8.05 (m, 3H), 7.18 (t, 1H), 8.31 (d, 1H).

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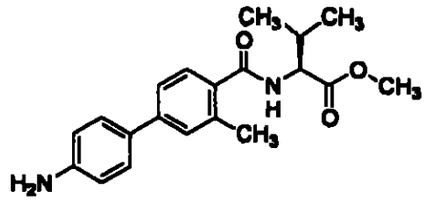
Paso 2. Preparación de N-[(3-metil-4'-nitrobifenil-4-il)carbonil]-L-valinato de metilo



Se disolvió ácido 3-metil-4'-nitrobifenil-4-carboxílico (0.50 g, 1.0 mmoles) en cloruro de metileno (10 ml) y luego se agregó cloruro de oxalilo (0.25 ml, 0.29 mmoles) seguido por una gota de DMF. La mezcla resultante se agitó a 50°C durante 45 min y luego se concentró bajo presión reducida. El residuo se disolvió en cloruro de metileno (5 ml) y se agregó por goteo a una mezcla enfriada en hielo de clorhidrato de éster metílico de L-valina (0.39 g, 2.3 mmoles), cloruro de metileno (10 ml) y trietilamina (1.08 mg, 7.75 mmoles). La solución resultante se agitó a ta durante 18 h. La mezcla se concentró bajo presión reducida, y el residuo se purificó por cromatografía en columna (50% EtOAc en hexanos). Esto dio 0.653 g (91%) del compuesto del título. CL/EM m/z 370.9 (MH^+), tiempo de retención 3.29 min. RMN ^1H (400 MHz, CD_2Cl_2) δ 1.06 (dd, 6H), 2.32-2.39 (m, 1H), 2.55 (s, 3H), 3.78 (s, 3H), 4.71-4.78 (m, 1H), 6.33 (d, 1H), 7.42-7.52 (m, 3H), 7.82 (d, 2H), 8.26 (d, 2H).

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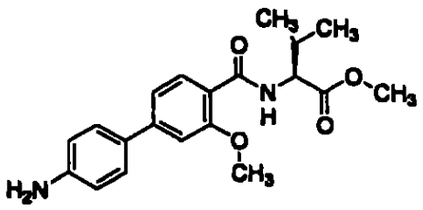
Paso 3. Preparación de N-[(4'-amino-3-metilbifenil-4-il)carbonil]-L-valinato de metilo



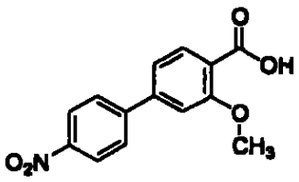
El polvo de hierro (0.79 g, 1.4 mmoles) se agregó a una solución de N-[(3-metil-4'-nitrobifenil-4-il)carboni]-L-valinato de metilo (0.65 g, 1.4 mmoles) en etanol (20 ml). Se agregó HCl concentrado (0.71 ml, 1.4 mmoles), y la mezcla se calentó a reflujo durante 1 h. Al enfriarse a Ta, la mezcla se filtró a través de una almohadilla de Celite®, y el filtrado se concentró a vacío. El material se purificó por cromatografía en columna (33% EtOAc en hexanos), dando 0.50 g (cuantitativa) del compuesto del título. CL(EM m/z 341.1 (MH^+), tiempo de retención 2.19 min. RMN ^1H (400 MHz, CD_2Cl_2) δ 1.06 (dd, 6H), 2.32-2.39 (m, 1H), 2.50 (s, 3H), 3.78 (s, 3H), 4.71-4.78 (m, 1H), 6.33 (d, 1H), 6.78 (d, 2H), 7.38-7.44 (m, 5H).

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Intermediario XIII-6: N-[(4'-amino-3-metoxibifenil-4-il)carbonil]-L-valinato de metilo



Paso 1. Preparación de ácido 3-metoxi-4'-nitrobifenil-4-carboxílico

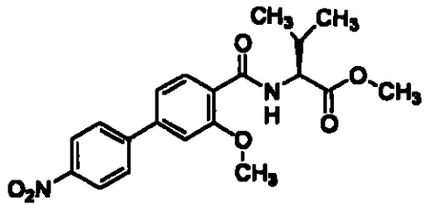


Se suspendió 3-metoxi-4'-nitrobifenil-4-carboxilato de metilo (0.35 g, 0.97 mmoles) en THF (6 ml), MeOH (6 ml) y agua (3 ml) y se agregó NaOH (0.19 g, 4.9 mmoles). La mezcla de reacción se calentó a 50°C durante 3 h. Al enfriar a ta, la mezcla de reacción se concentró bajo presión reducid y se acidificó con HCl 2N. El sólido resultante se recuperó por filtración y se secó en un horno a vacío de 40°C, dando 0.28 g (cuantitativo) del compuesto del título. RMN ^1H (400 MHz,

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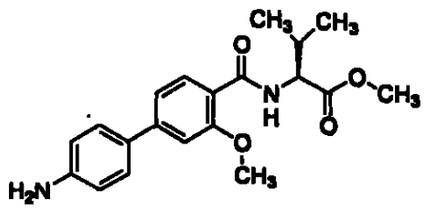
DMSO-d_6) δ 3.90 (s, 3H), 7.35-7.41 (m, 2H9, 7.77 (d, 1H), 8.03 (d, 2H9, 8.36 (d, 2H).

Preparación de N-[(3-metoxi-4'-nitrobifenil-4-il)carbonil]-L-valinato de metilo



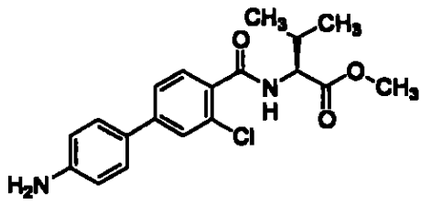
Se disolvió ácido 3-metoxi-4'-nitrobifenil-4-carboxílico (0.28 g, 1.0 mmoles) en cloruro de metileno 810 ml), y luego se agregó cloruro de oxalilo (0.13 ml, 1.51 mmoles), seguido por una gota de DMF. La mezcla resultante se agitó a 50°C durante 45 min y luego se concentró bajo presión reducida. El residuo se disolvió en cloruro de metileno (0.21 g, 1.2 mmoles), cloruro de metileno (10 ml) y trietilamina (0.57 ml, 4.1 mmoles). La solución resultante se agitó a ta durante 18 h. La mezcla se concentró bajo presión reducida, y el residuo se purificó por cromatografía en columna (33% EtOAc en hexanos). CL/EM m/z 387.0 (MH^+), tiempo de retención 3.40 min. RMN ^1H (400 MHz, CD_2Cl_2) δ 1.05 (t, 6H), 2.32-2.39 (m, 1H), 3.78 (s, 3H), 4.10 (s, 3H), 4.71-4.78 (m, 1H), 7.22 (s, 1H), 7.38 (d, 1H), 7-80 (d, 2H), 8.22-8.37 (m, 4H).

Paso 3. Preparación de N-[(4'-amino-3-metoxibifenil-4-il)carbonil]-L-valinato de metilo



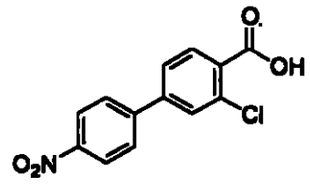
Se agregó polvo de hierro (0.35 g, 6.2 mmoles) a una solución de N-[(3-metoxi-4'-nitrobifenil-4-il)carbonil]-L-valinato de metilo (0.30 g, 0.62 mmoles) en etanol (10 ml). Se agregó HCl concentrado (0.31 ml, 0.62 mmoles), y la mezcla se calentó a reflujo durante 1 h. Al enfriar a ta, la mezcla se filtró a través de una almohadilla de Celite®, y el filtrado se concentró a vacío. El material se purificó por cromatografía en columna (33% EtOAc en hexanos), dando 0.296 g (cuantitativo) del compuesto del título. CL/EM m/z 357.2 (MH^+), tiempo de retención 2.34 min.

Intermediario XIII-7: N-[(4'-amino-3-clorobifenil-4-il)carbonil]-L-valinato de metilo



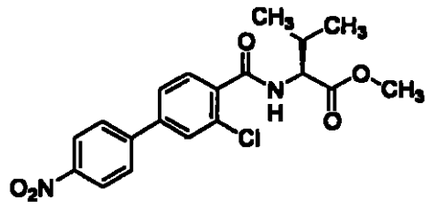
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Paso 1. Preparación de ácido 3-cloro-4'-nitrobifenil-4-carboxílico



Se suspendió 3-cloro-4'-nitrobifenil-4-carboxilato de metilo (0.50 g, 1.4 mmoles) se suspendió en THF (6 mL), MeOH (6 ml) y agua (3 ml) y se agregó NaOH (0.27 g, 6.9 mmoles). La mezcla de reacción se calentó a 50°C durante 3 h. Al enfriarse a ta, la mezcla de reacción se concentró bajo presión reducida y se acidificó con HCl 2N. El sólido resultante se recuperó por filtración y se secó en un horno de vacío a 40°C, dando 0.315 g (83%) del compuesto del título. RMN ^{1}H (400 MHz, DMSO-d_6) δ 7.81-8.10 (m, 5H), 8.21-8.38 (m, 2H).

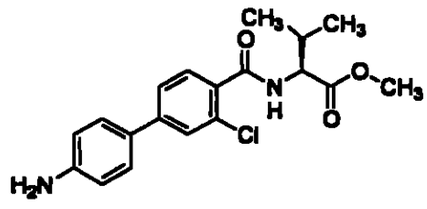
Paso 2. Preparación de N-[(3-cloro-4'-nitrobifenil-4-il)carbonil]-L-valinato de metilo



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Se disolvió ácido 3-cloro-4'-nitrobifenil-4-carboxílico (0.31 g, 1.12 mmoles) en cloruro de metileno (10 ml), y luego se agregó cloruro de oxalilo (0.15 ml, 1.7 mmoles), seguido por una gota de DMF. La mezcla resultante se agitó a 50°C durante 45 min y luego se concentró bajo presión reducida. El residuo se disolvió en cloruro de metileno (5 ml) y se agregó por goteo a una mezcla enfriada en hielo de clorhidrato de éter metílico de L-valina (0.22 g, 1.3 mmoles), cloruro de metileno (10 ml) y trietilamina (0.62 ml; 4.5 mmoles). La solución resultante se agitó a ta durante 18 h y luego se concentró bajo presión reducida. El residuo se recogió en EtOAc, se pasó a través de un tapón de gel de sílice y se concentró bajo presión reducida. Esto dio 0.305 g (70%) del compuesto del título. CL/EM m/z 390.9 (MH^+), tiempo de retención 3.30 min. RMN ^1H (400 MHz, CD_2Cl_2) δ 1.06 (dd, 6H), 2.32-2.39 (m, 1H), 3.80 (s, 3H9, 4.71-4.78 (m, 1H), 6.33 (d, 1H), 6.76 (d, 2H), 7.58-7.80 (m, 5H), 8.35 (d, 2H9.

Paso 3. Preparación de N-[(4'-amino-3-clorobifenil-4-il)carbonil]-L-valinato de metilo

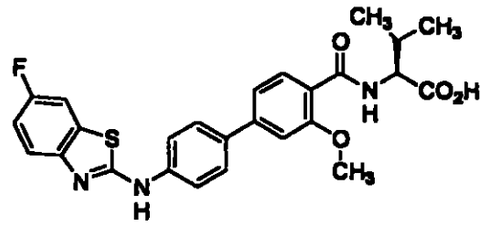


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Se agregó polvo de hierro (0.44 g, 7.8 mmoles) a una solución de N-[(3-cloro-4'-nitrobifenil-4-il)carbonil]-L-valinato de metiio (0.30 g, 0.78 mmoles) en etanol (10 ml). Se agregó HCl concentrado (0.39 ml, 0.78 mmoles), y la mezcla se calentó a reflujo durante 3 h. Al enfriarse a ta, la mezcla se filtró a través de una almohadilla de Celite® y el filtrado se concentró a vacío. El material se purificó por cromatografía en columna (33% EtOAc en hexanos), dando 0.25 g (89%) del compuesto del título. CL/EM m/z #61.2 (MH^+), tiempo de retención 2.36 min. RMN ^1H (400 MHz, CD_2Cl_2) δ 1.06 (dd, 6H), 2.32-2.39 (m, 1H), 3.80 (s, 3H), 4.71-4.78 (m, 1H), 6.82 (d, 3H), 7.40-7.74 (m, 5H).

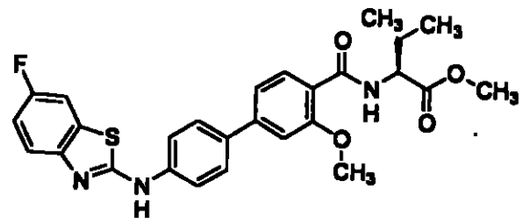
Preparación de Compuestos de la Formula (I) por el Método C

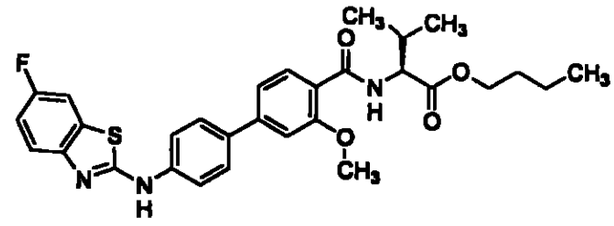
Ejemplo 60: N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il)carbonil]-L-valina



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Paso 1.Preparación de N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxi bifenil-4-il}carbonil)-L-valinato de metilo y N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-valinato de butilo



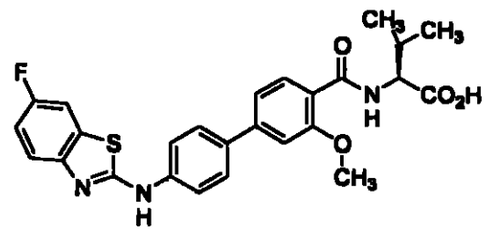


Una mezcla de N-[(4'-amino-3-metoxibifenil-4-il)carbonil]-L-valinato de metilo (0.05 g, 0.14 mmoles), 2-cloro-6-fluorobenzotiazol (0.03 g, 0.14 mmoles), y 1-butanol (1.5 ml) se calentó a 60-70°C y luego HCl 4N en 1,4-dioxano (0.02 ml, 0.07 mmoles) se agregó con agitación. La mezcla de reacción se calentó a 90°C durante 18 h. Al enfriarse a ta, la mezcla de reacción se concentró bajo presión reducida y se purificó por CLAR (40-90% CH_3CN en gradiente de H_2O/0.1% TFA). Esto dio 7 mg (10%) de N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-

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valinato de metilo y 39 mg (51%) de N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-valinato de butilo.

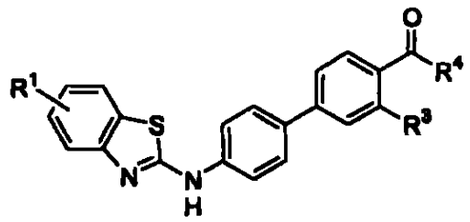
Paso 2. Preparación de N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il]carbonil)-L-valina



N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-valinato de butilo (0.02 g, 0.03 mmoles) se suspendió en THF (1 ml), MeOH (1 ml) y agua (0.5 ml) y luego se agregó LiOH (0.01 g, 0.35 mmoles). La mezcla de reacción se calentó a 50°C durante 3 h. Al enfriar ta, la mezcla de reacción se concentró bajo presión reducida y se acidificó con HCl 2N. El sólido resultante se recuperó por filtración y se purificó por CLAR (15-.80% CH_3CN en gradiente de H_2O/TFA 0.1%), dando 19 mg (91%) del compuesto del título. CL/EM m/z 494.1 (MH^+), tiempo de reacción 3.47 min. RMN ^1H (400 MHz, CD_3OD) δ 1.06 (d, 6H), 2.32-2.39 (m, 1H), 4.10 (s, 3H), 4.60 (d, 1H), 7.05

(t, 1H), 7.35-7.58 (n, 4H), 7.60 (d, 2H), 7.80 (d, 2H), 8.05 (d, 1H).

Tabla 3a. Ejemplos Preparativos de Compuestos de la Fórmula (I) por el Método C



Ejemplo No.	R^1	R^3	R^4	CL-EM Tpo. Ret. (min)	CL-EM $[M+H]^+$
60	6-F	OCH_3	L-Val-OH	3.50	494.1
61	6-F	CH_3	L-Val-OH	3.39	478.2
62	6-OCH_3	CH_3	L-Val-OH	3.21	490.2
63	H	CH_3	L-Val-OH	3.24	460.2
64	6-i-Pr	CH_3	L-Val-OH	3.65	502.2
65	6-Cl	CH_3	L-Val-OH	3.59	494.2

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Ejemplo No.	R^1	R^3	R^4	CL-EM Tpo. Ret. (min)	CL-EM $[M+H]^+$
66	7-F	CH_3	L-Val-OH	3.47	478.2
67	7-Cl	CH_3	L-Val-OH	3.62	494.2
68	H	OCH_3	L-Val-OH	3.37	476.1
69	H	H	L-Val-OH	3.39	446.2
70	H	H	D-Val-OH	3.21	446.2
71	6-Cl	OCH_3	L-Val-OH	3.71	510.2
72	7-F	OCH_3	L-Val-OH	3.56	494.2
73	7-Cl	OCH_3	L-Val-OH	3.71	510.1
74	6-i-Pr	OCH_3	L-Val-OH	3.77	518.2
75	H	Cl	L-Val-OH	3.36	480.2
76	6-i-Pr	Cl	L-Val-OH	3.73	522.2
77	6-Cl	Cl	L-Val-OH	3.67	550.9
78	7-F	Cl	L-Val-OH	3.53	498.1
79	7-Cl	Cl	L-Val-OH	3.68	514.1
80	H	OCH_3	L-Leu-OH	3.87	490.3
81	6-OCH_3	OCH_3	L-Leu-OH	3.85	520.3
82	6-Cl	OCH_3	L-Leu-OH	4.19	524.3
83	4-Cl, 6-F	OCH_3	L-Leu-OH	4.21	542.1
84	6-NO_2	OCH_3	L-Leu-OH	3.98	535.0
85	6-$(CH_3)SO_2$	OCH_3	L-Leu-OH	3.54	568.2
86	6-i-Pr	OCH_3	L-Leu-OH	4.24	532.3

Tabla 3b. Nombres de la IUPAC de Compuestos en la Tabla 3a

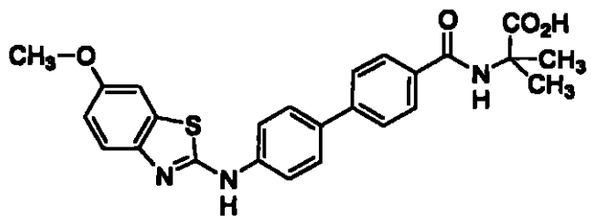
Ejemplo No.	Nombre de IUPAC
60	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-valina
61	N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-valina

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Ejemplo No.	Nombre de IUPAC
62	N-({4'-[(6-metoxi-il}carbonil)-L-valina 1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-
63	N-{[4'-(1,3-benzotiazol-2-ilamino)-3-metilbifenil-4-il]carbonil}-L- valina
64	N-({4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4- il}carbonil)-L-valina
65	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4- il}carbonil)-L-valina
66	N-({4'-[(7-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4- il}carbonil)-L-valina
67	N-({4'-[(7-cloro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4- il}carbonil)-L-valina
68	N-{[4'-(1,3-benzotiazol-2-ilamino)-3-metoxibifenil-4-il]carbonil}-L- valina
69	N-{[4'-(I,3-benzotiazol-2-ilamino)bifenil-4-il]carbonil}-L-valina
70	N-{[4'-(1,3-benzotiazol-2-ilamino)bifenil-4-il]carbonil}-D-valina
71	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4- il}carbonil)-L-valina
72	N-({4'-[(7-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4- il}carbonil)-L-valina
73	N-({4'-[(7-cloro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4- il}carbonil)-L-valina
74	N-({4'-[(6-isopropil -1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4- il}carbonil)-L-valina
75	N-{[4'-(1,3-benzotiazol-2-ilamino)-3-clorobifenil-4-il]carbonil}-L- valina
76	N-({3-cloro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-valina
77	N-({3-cloro-4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-valina
78	N-({3-cloro-4'-[(7-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-valina
79	N-({3-cloro-4'-[(7-cloro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-valina
80	N-{[4'-(1,3-benzotiazol-2-ilamino)-3-metoxibifenil-4-il]carbonil}-L- leucina
81	N-({3-metoxi-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-leucina

Ejemplo No.	Nombre de IUPAC
82	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4- il}carbonil)-L-leucina
83	N-({4'-[(4-cloro-6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-leucina
84	N-({3-metoxi-4'-[(6-nitro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-leucina
85	N-[(3-metoxi-4'-{[6-(metilsulfonil)-1,3-benzotiazol-2- il]amino}bifenil-4-il)carbonil]-L-leucina
86	N-({4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4- il}carbonil)-L-leucina

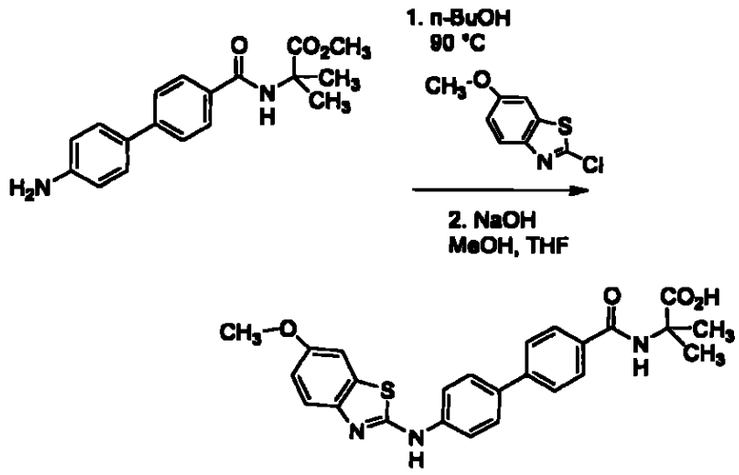
Ejemplo 87: N({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-2-metilalanina



La preparación de N-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-bifenil-4-il]carbonil)-2-metilalanina se describe más delante del Esquema de Reacción 12.

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Esquema de Reacción 12



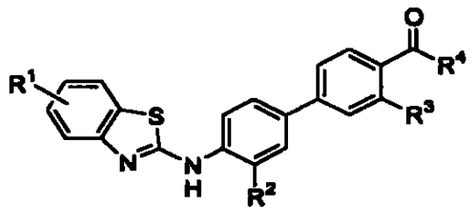
Como se muestra en el Esquema de Reacción 12, una mezcla de N-[(4'-aminobifenil-4-il)carbonil]-2-metilalaninato de metilo (100 mg, 0.32 mmoles), 2-cloro-6-metoxibenzotiazol (83 mg, 0.42 mmoles; comercialmente disponible), y 1-butanol (4.0 ml) se calentó a 90°C durante la noche. El solvente se evaporó bajo presión reducida para dar N-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-2-metilalaninato de metilo crudo; CL-EM m/z 476.2 (MH^+), tiempo de retención 3.25 minutos.

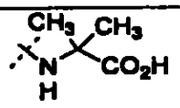
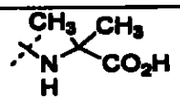
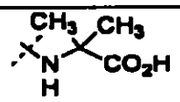
El aminobenzotiazol intermediario se disolvió en metanol (0.4 ml) y tetrahidrofurano (0.4 ml). Se agregó solución de NaOH acuosa (2N, 0.64 ml, 1.28 mmoles) y la mezcla se agitó a ta durante la noche. La mezcla se filtró y el filtrado se purificó por CLAR de fase inversa preparativa (gradiente de agua/acetonitrilo, conteniendo 0.1% TFA) para

dar N-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-bifenil-4-il}carbonil)-2-metilalanina (58 mg, 39%). RMN ^{1}H (400 MHz, DMSO-d_6) δ 1.47 (s, 6H), 3.78 (s, 3H), 6.95 (d, 1H), 7.24 (s, 1H), 7.32 (d, 1H), 7.72-7.78 (m, 4H), 7.88 (d, 2H), 7.92 (d, 2H), 8.47 (s, 1H), 10.27 (s, 1H); CL-EM m/z 462.5 (MH^+), tiempo de retención 2.94 minutos.

Usando los métodos descritos antes y sustituyendo los materiales de partida apropiados, los compuestos de la Fórmula (I) listados en la siguiente Tabla 4a, se prepararon similarmente.

Tabla 4a. Ejemplos Preparativos de Compuestos de la Formula (I) por el Método C



Ejemplo No.	R^1	R^2	R^3	R^4	CL-EM Tpo. Ret. (min)	CL-EM $[M+H]^+$
87	6-OMe	H	H		2.94	462.4
88	H	H	H		2.98	432.2
89	6-Cl	H	H		3.31	466.5

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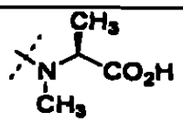
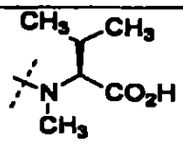
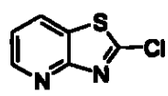
Ejemplo No.	R^1	R^2	R^3	R^4	CL-EM Tpo. Ret. (min)	CL-EM $[M+H]^+$
90	H	H	H		3.09	432.2
91	H	H	H		3.33	460.2

Tabla 4b. Nombres de IUPAC de Compuestos en la Tabla 4a

Ejemplo No.	Nombre IUPAC
87	N-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-2-metilalanina
88	N-{[4'-(1,3-benzotiazol-2-ilamino)bifenil-4-il]carbonil}-2-metilalanina
89	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-2-metilalanina
90	N-{[4'-(1,3-benzotiazol-2-ilamino)bifenil-4-il]carbonil}-N-metil-L-alanina
91	N-{[4'-(1,3-benzotiazol-2-ilamino)bifenil-4-il]carbonil}-N-metil-L-valina

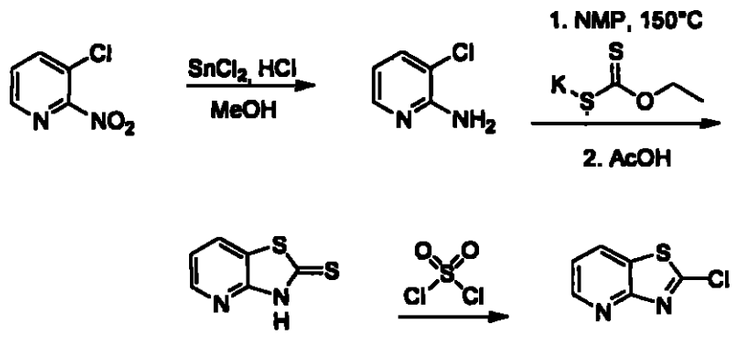
Preparación de Intermediario V-1: 2-cloro[1,3]tiazolo[4,5-b]piridina



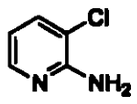
La preparación de 2-cloro[1,3]tiazolo[4,5-b]piridina se describe después del Esquema de Reacción 13.

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Esquema de Reacción 13



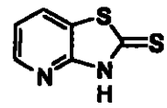
Paso 1: Preparación de 2-amino-3-cloropiridina



Una muestra de 3-cloro-2-nitropiridina (1.00 g, 6.31 mmoles) se disolvió en metanol (10 ml), se trató con cloruro de Estaño (II) (5.98 g, 31.54 mmoles) seguido por HCl concentrado (2.63 ml, 31.54 mmoles). La mezcla de reacción se dejó agitar durante la noche a ta. La solución luego se diluyó con acetato de etilo y se lavó con solución de NaOH 1N. La fase orgánica luego se lavó con solución de $NaHCO_3$ concentrada y se secó sobre Na_2SO_4. La concentración a vacío dio el compuesto del título (510.0 mg, 63%). RMN ^1H (400 MHz, CD_3CN) δ 6.80 (m, 1H), 7.60 (d, 1H), 8.12 (d, 1H).

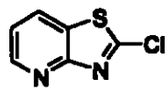
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Paso 2: Preparación de [1,3]tiazolo[4,5-b]piridina-2(3H)-tiona



El intermediario 2-amino-3-cloro-piridina (510 mg, 3.97 mmoles) se disolvió en 1-metil-2-pirrolidinona (7 ml) y se trató con etil xantato de potasio (953.9 mg, 5.95 mmoles). La solución se calentó a 150°C durante la noche. La solución se enfrió luego a ta y se trató con ácido acético glacial (1 ml) y se diluyó con agua (150 ml). El precipitado resultante se filtró y trituró con solución de agua/etanol 1:1. La torta de filtro se suspendió luego en EtOAc. La concentración a vacío dio el compuesto del título (650.0 mg, 97%). RMN ^{1}H (400 MHz, DMSO-d_6) δ 7.25 (m, 1H), 8.11 (d, 1H), 8.35 (d, 1H).

Paso 3. Preparación de 2-cloro[1,3]tiazolo[4,5-b]piridina



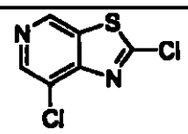
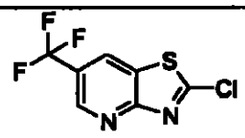
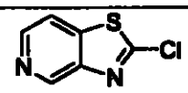
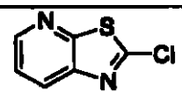
El intermediario [1,3]tiazolo[4,5-b]piridina-2(3H)-tiona (644.0 mg, 3.83 mmoles, polvo seco) se trató con cloruro de sulfurilo puro (3.08 ml, 38.28 mmoles) y se dejó

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agitar a ta durante la noche. La mezcla de reacción se enfrió con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con NaOH 1N, seguido por salmuera, y se secó sobre Na_2SO_4. La concentración a vacío dio el compuesto del título (260.0 mg, 40%). CL/EM m/z 171.2 (MH^+); tiempo de retención 1.55 min. RMN ^1H (400 MHz, DMSO-d_6) δ 7.58 (m, 1H), 8.62 (d, 1H), 8.78 (d, 1H).

Los siguientes intermediarios de la Fórmula (V) se prepararon usando el método anterior y cloro-nitro-piridina comercialmente disponible apropiado como el material de partida.

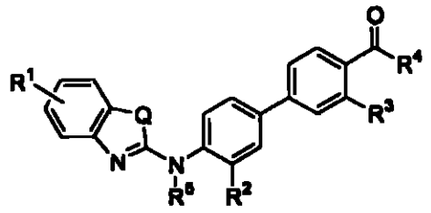
Tabla 5. Ejemplos de Compuestos de la Fórmula (V)

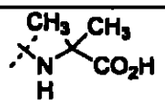
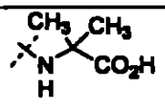
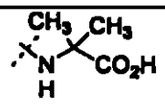
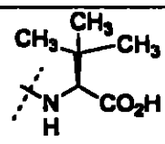
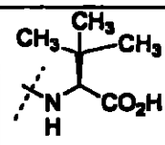
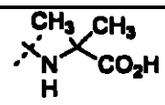
Ejemplo	Estructura	CL/EM *m/z*(MH^+)	Tpo. Ret. (min)
Intermediario V-2		205.2	2.24
Intermediario V-3		239.4	2.64
Intermediario V-4		171.2	1.15
Intermediario V-5		171.2	2.13

Usando los métodos descritos en los procedimientos provistos en la presente y sustituyendo los materiales de

partida apropiados, compuestos de la Fórmula (I), listados en la Tabla 6 pueden prepararse similarmente.

Tabla 6. Ejemplos de Compuestos de la Fórmula (I)

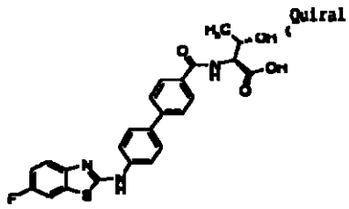
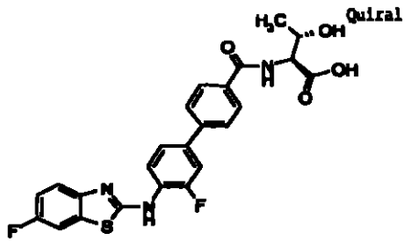
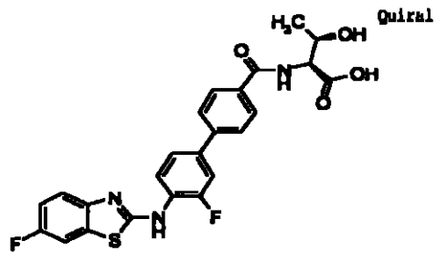
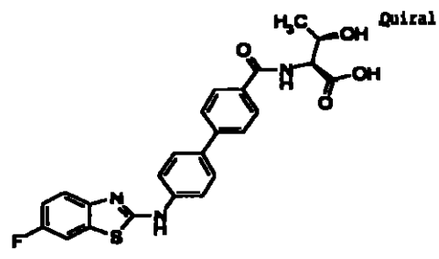


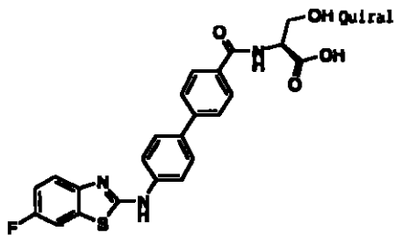
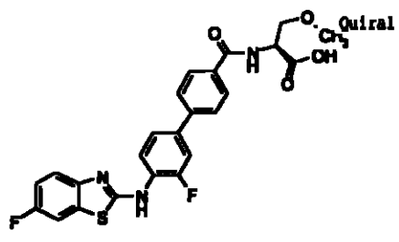
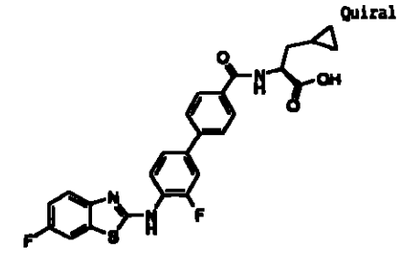
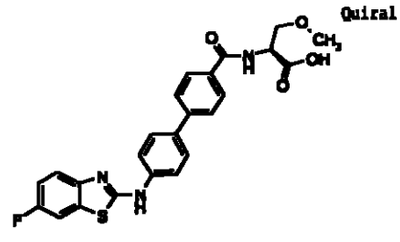
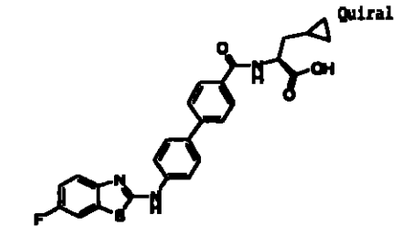
Ejemplo No.	Q	R^1	R^2	R^3	R^4	R^5
92	NH	H	H	H		H
93	NH	6-F	F	H		H
94	O	6-F	F	H		H
95	S	6-OMe	H	CH_3		CH_3
96	O	6-CF_3	F	H	L-Leu-OH	CH_3
97	O	5-CH_3	F	H	L-Val-OH	CH_3
98	O	5-Cl	H	Cl		CH_3
99	S	6-F	F	H		CH_2CH_2OH

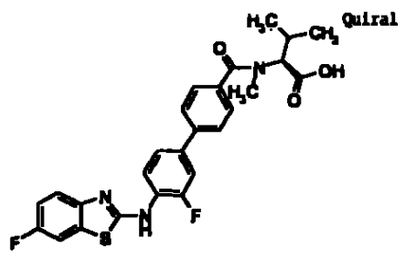
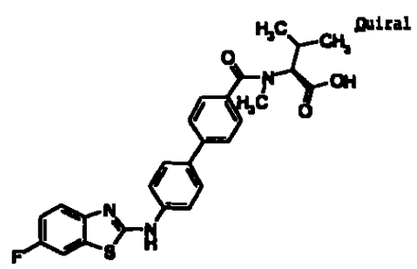
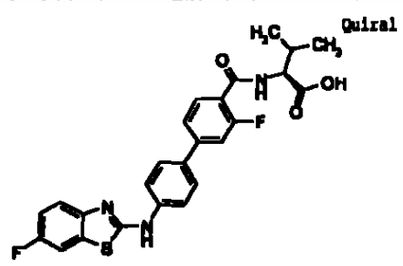
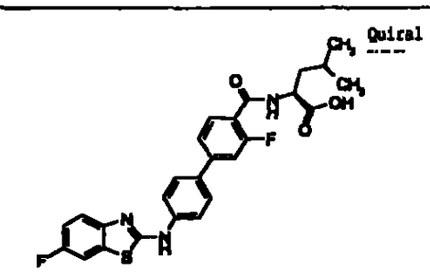
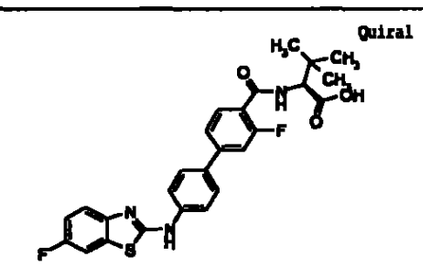
Usando los métodos descritos en los procedimientos provistos en la presente y sustituyéndolos materiales de

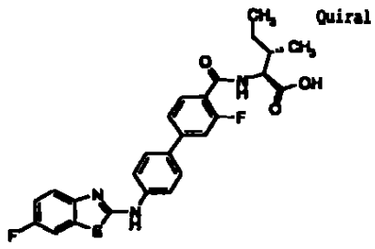
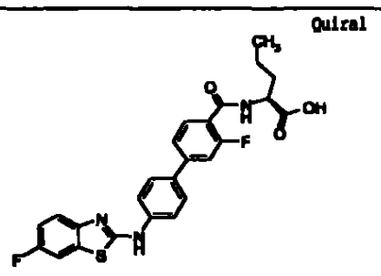
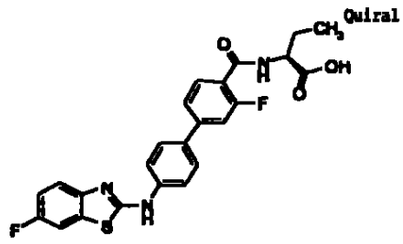
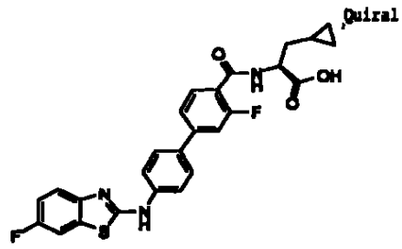
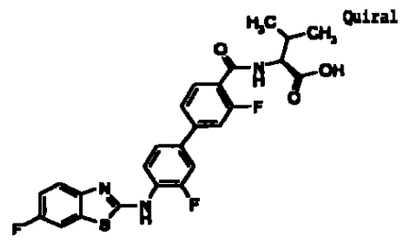
partida apropiados, se prepararon compuestos de la Fórmula (I), listados en la Tabla 7.

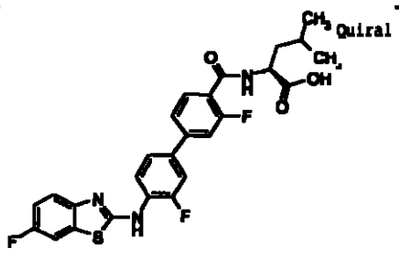
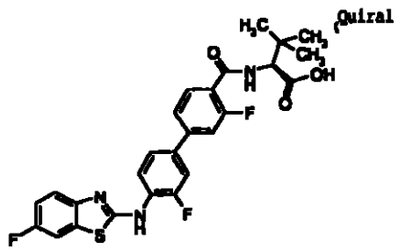
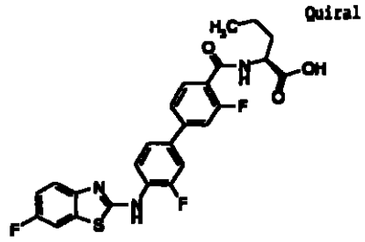
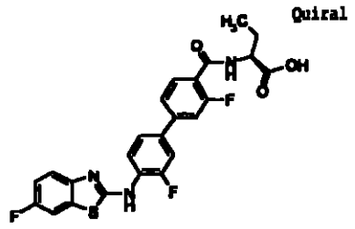
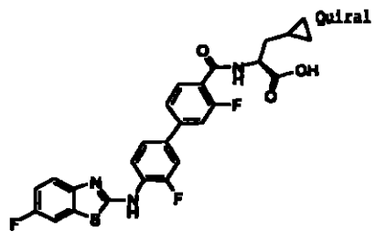
Tabla 7a. Ejemplos de Compuestos

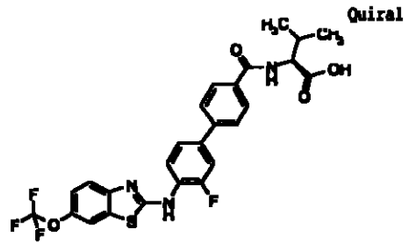
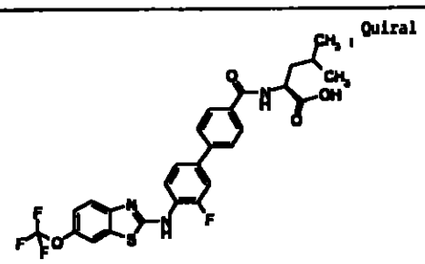
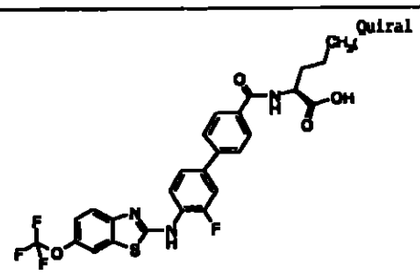
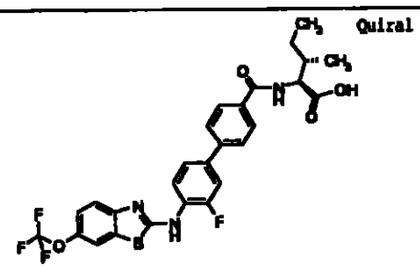
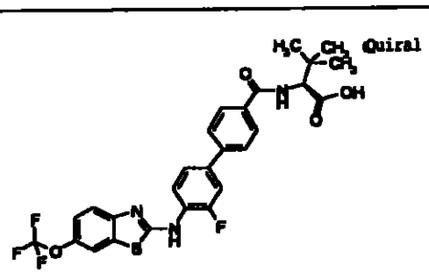
Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	Cl-EM [M+H]+	Método
100		2.97	466.1	A
101		3.04	484.1	A
102		3.03	484.1	A
103		2.97	466.1	A

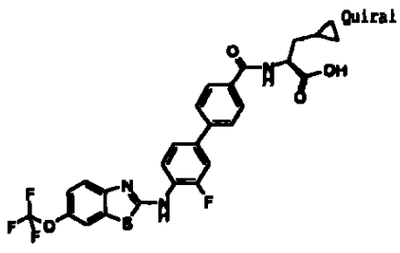
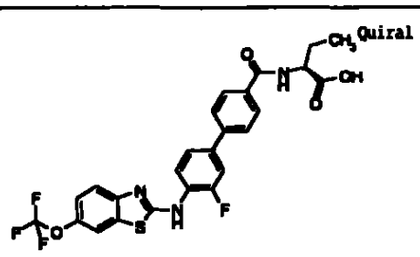
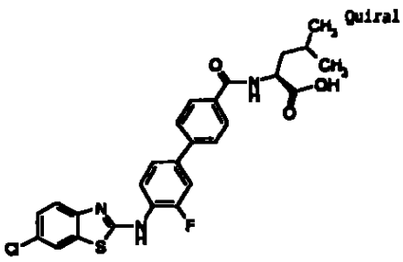
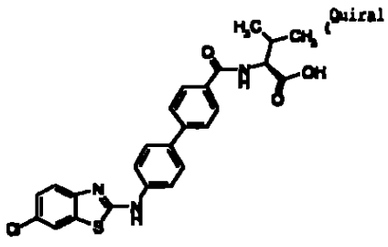
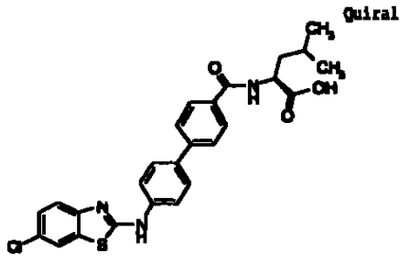
Ejemplo No.	Estructura	CL-EM T. Ret. (min)	CL-EM [M+H]+	Método
104		2.88	452.1	A
105		3.19	484.1	A
106		3.48	494.1	A
107		3.14	466.1	A
108		3.41	476.2	A

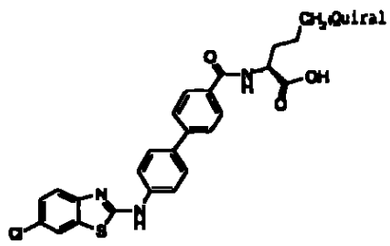
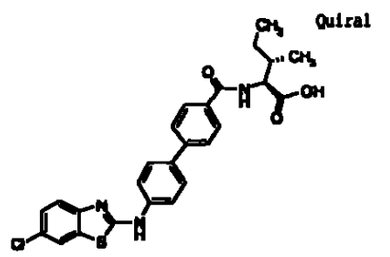
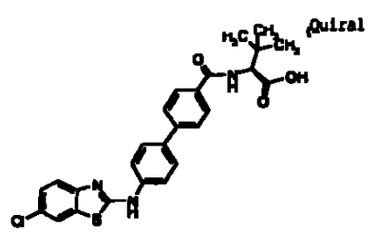
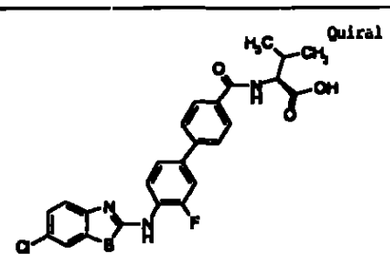
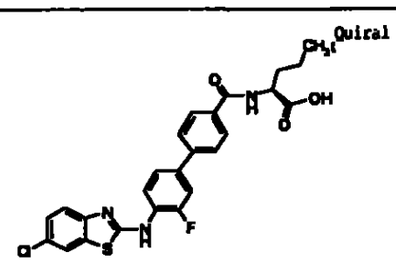
Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]	Método
109		3.53	496.1	A
110		3.43	478.2	A
111		3.52	482.2	A
112		3.66	496.2	A
113		3.66	496.2	A

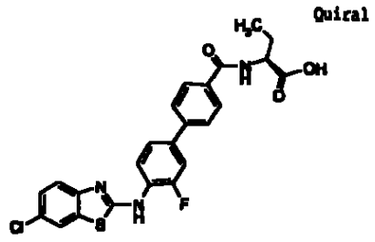
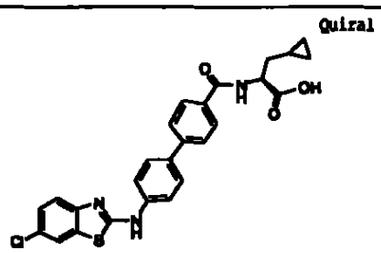
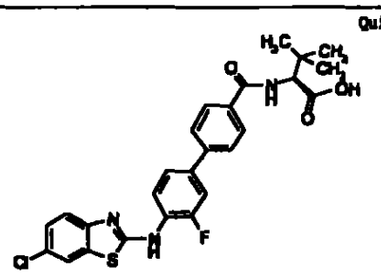
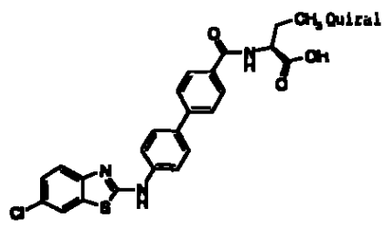
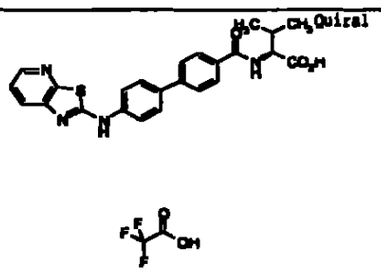
Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
114		3.67	496.2	A
115		3.53	482.2	A
116		3.39	468.2	A
117		3.56	494.2	A
118		3.6	500.2	A

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
119		3.72	514.2	A
120		3.74	514.2	A
121		3.61	500.1	A
122		3.47	485.1	A
123		3.64	512.1	A

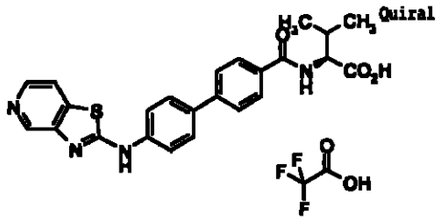
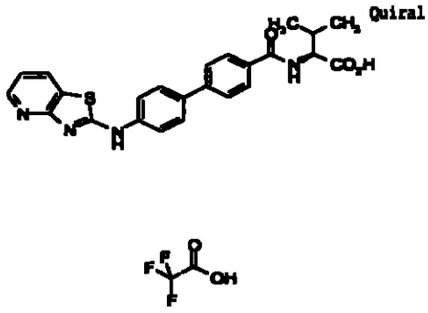
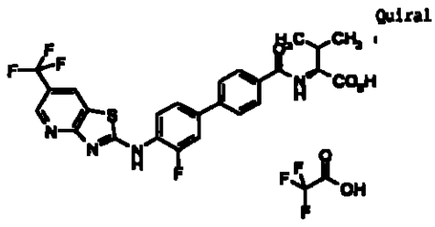
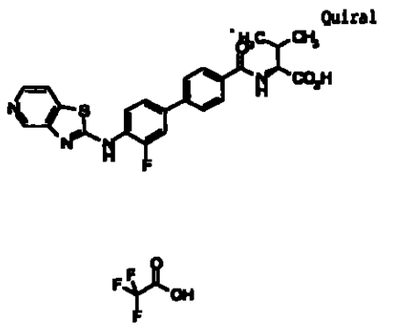
Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
124	 Quiral	4.27	548.2	A
125	 Quiral	4.56	562.2	A
126	 Quiral	4.23	562.1	A
127	 Quiral	4.56	562.1	A
128	 Quiral	4.45	562.2	A

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
129		4.47	560.2	A
130		4.28	534.1	A
131		3.79	512.1	A
132		3.57	480.1	A
133		3.71	494.1	A

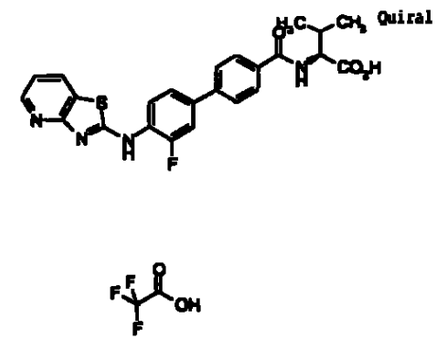
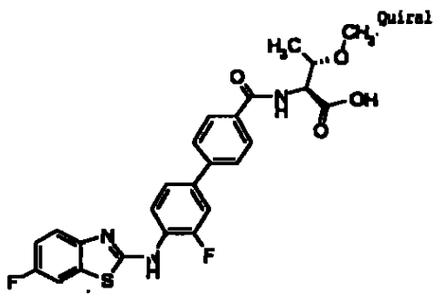
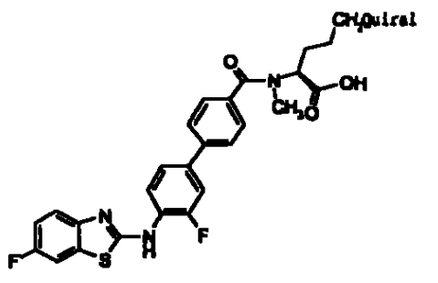
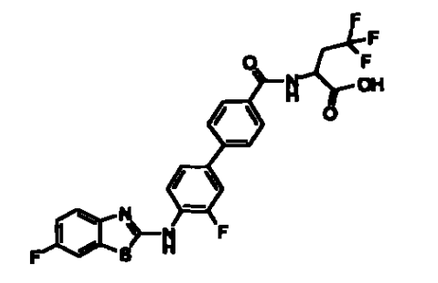
Ejemplo No.	Estructura	CL-EM T. Ret. (min)	CL-EM [M+H]+	Método
134		3.59	480.1	A
135		3.71	494.1	A
136		3.7	494.1	A
137		3.63	498.1	A
138		3.65	498.1	A

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
139		3.51	484.1	A
140		3.61	492.1	A
141		3.78	512.1	A
142		3.44	466.1	A
143		2.95	447.2	C

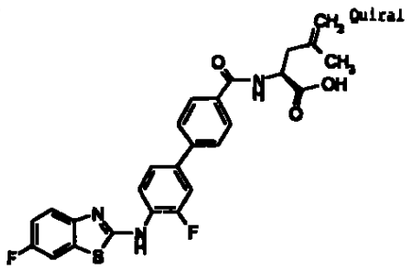
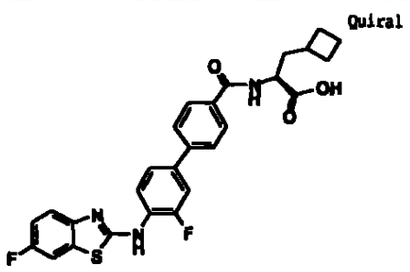
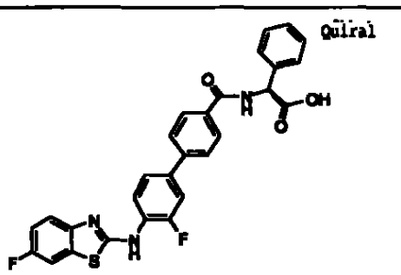
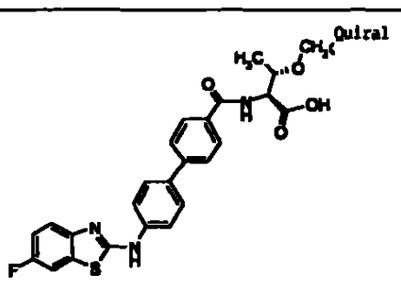
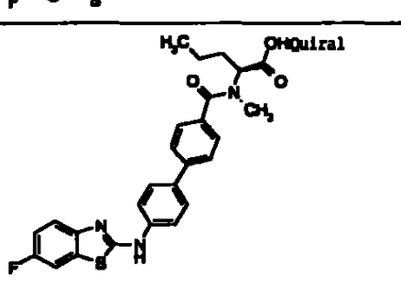
254

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
144	 Quiral	2.23	447.2	C
145	 Quiral	2.35	447.2	C
146	 Quiral	3.32	533.2	C
147	 Quiral	2.25	465.2	C

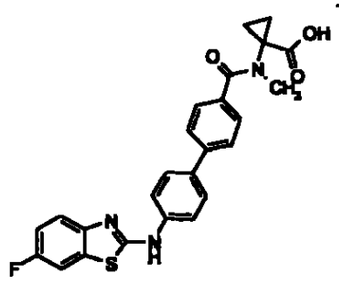
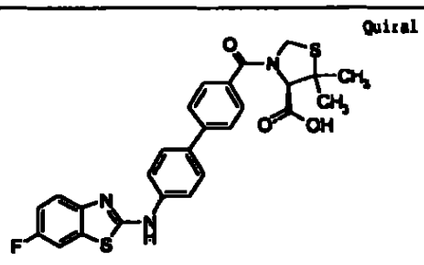
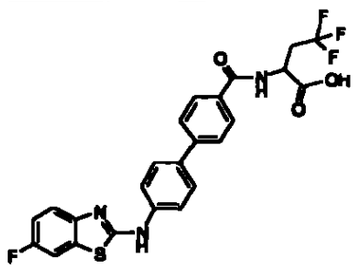
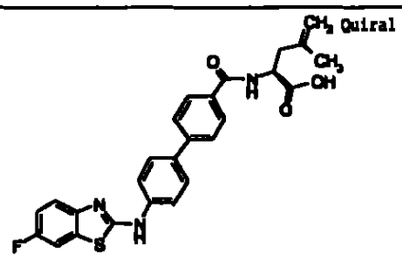
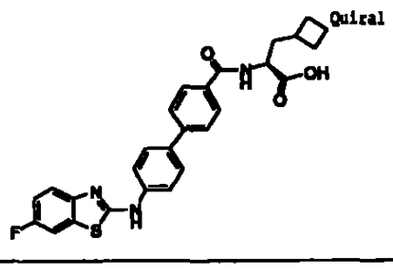
255

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
148		2.42	465.2	C
149		3.27	498.1	A
150		3.53	496.1	A
151		3.49	522.2	A

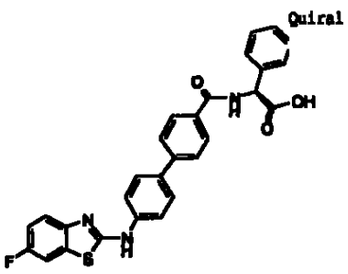
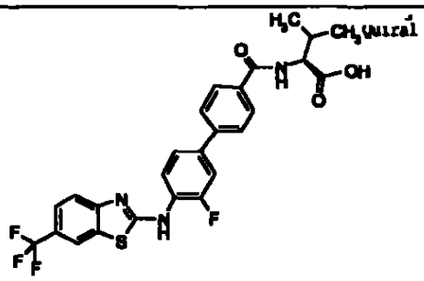
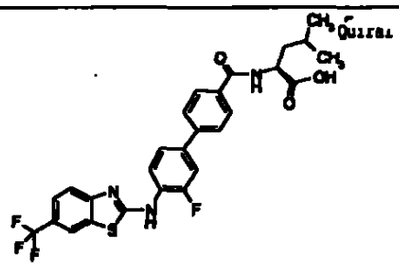
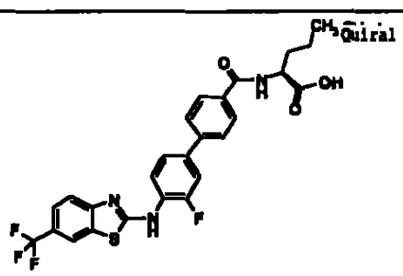
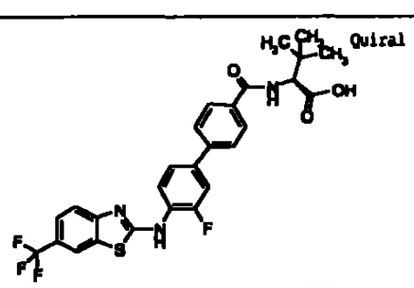
256

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
152		3.51	494.1	A
153		3.67	508.2	A
154		3.54	516.1	A
155		3.24	480.2	A
156		3.46	478.2	A

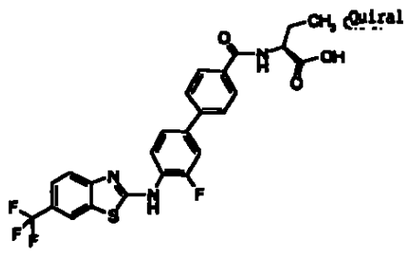
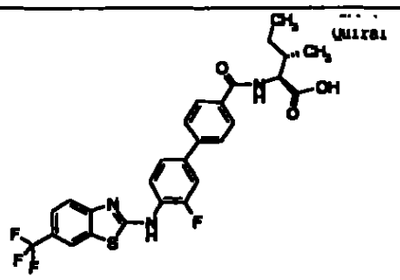
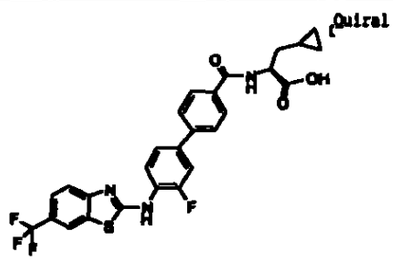
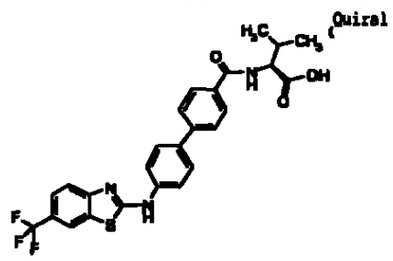
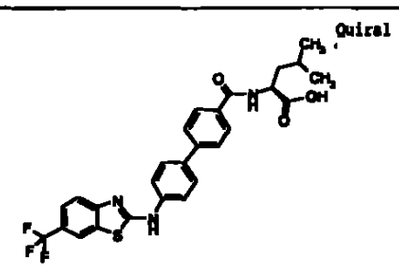
257

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
157		3.16	462.1	A
158	 Quiral	3.55	508.1	A
159		3.41	504.1	A
160	 Quiral	3.42	476.2	A
161	 Quiral	3.59	490.2	A

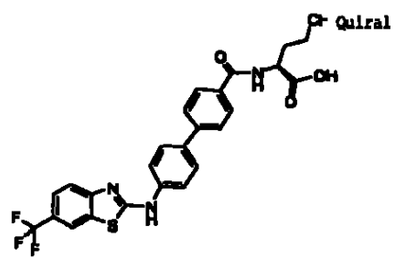
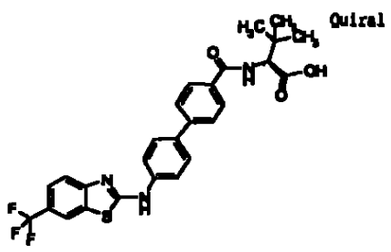
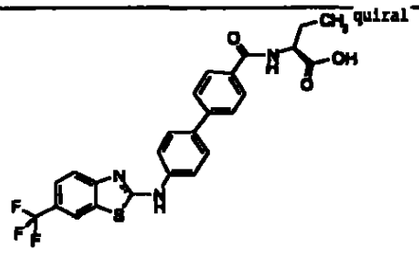
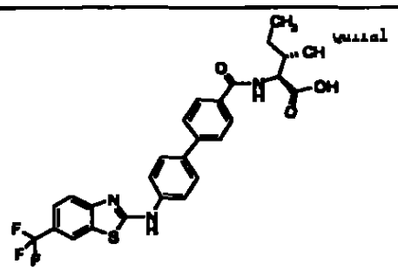
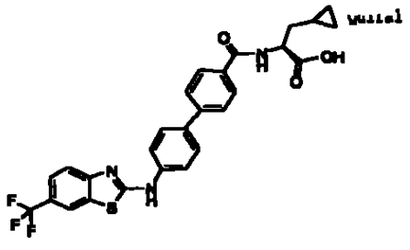
258

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM (M+H)+	Método
162		3.47	498.2	A
163		3.72	532.2	A
164		3.87	546.2	A
165		3.74	532.2	A
166		3.84	546.2	A

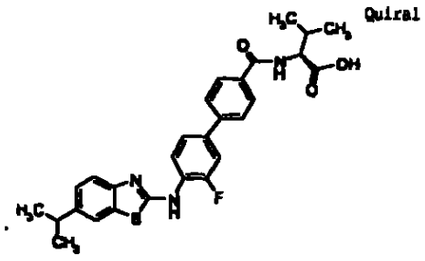
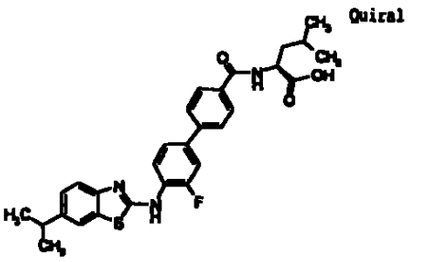
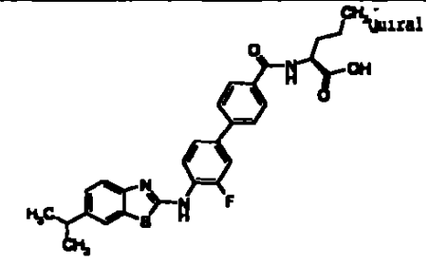
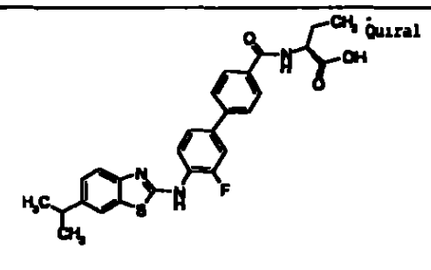
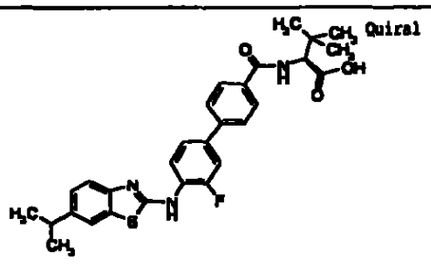
259

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
167		3.6	518.2	A
168		3.86	546.2	A
169		3.74	544.2	A
170		3.66	514.2	A
171		3.79	528.2	A

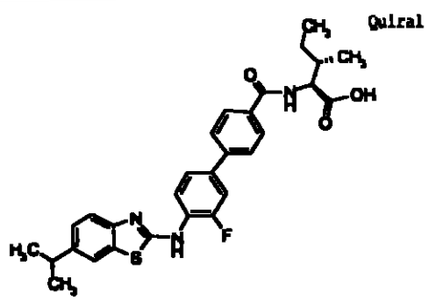
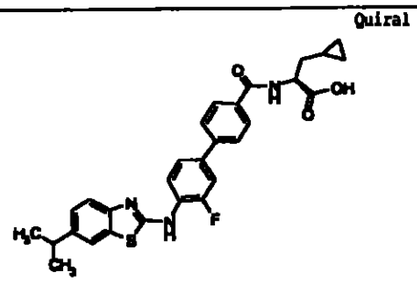
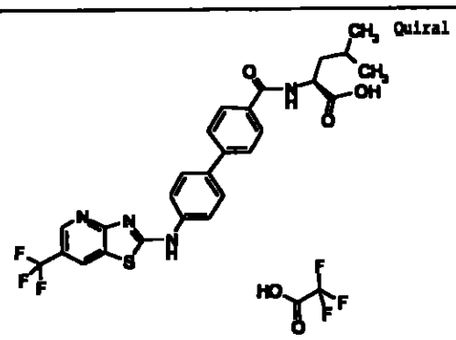
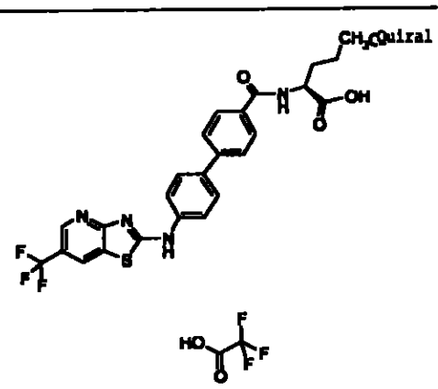
260

Ejemplo No.	Estructura	CL-EM Tpo.Ret.(min)	CL-EM [M+H]+	Método
172		3.68	514.2	A
173		3.77	528.2	A
174		3.54	500.2	A
175		3.78	528.2	A
176		3.68	526.2	A

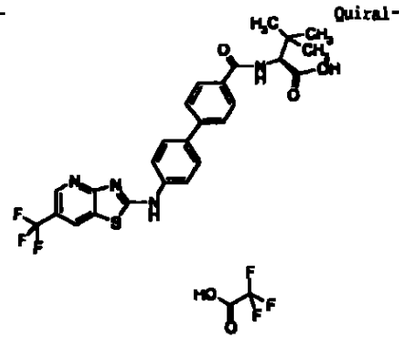
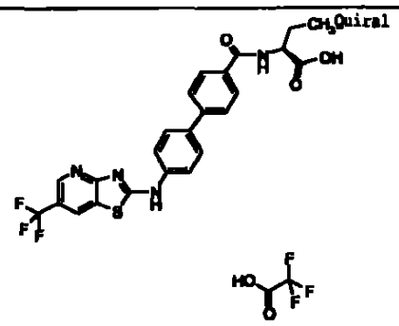
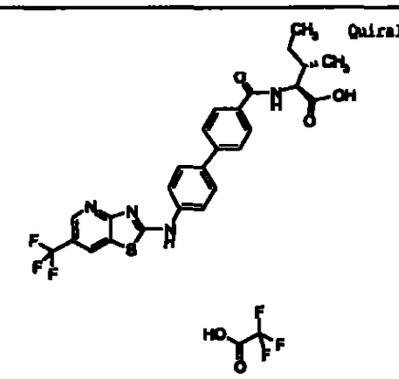
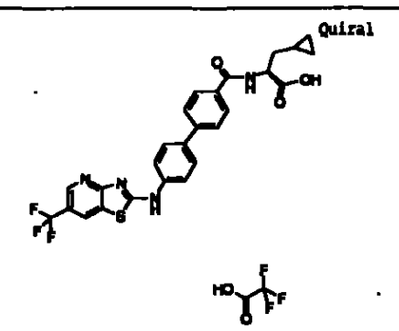
201

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
177		3.74	506.2	A
178		3.88	520.2	A
179		3.75	506.2	A
180		3.62	492.2	A
181		3.87	520.2	A

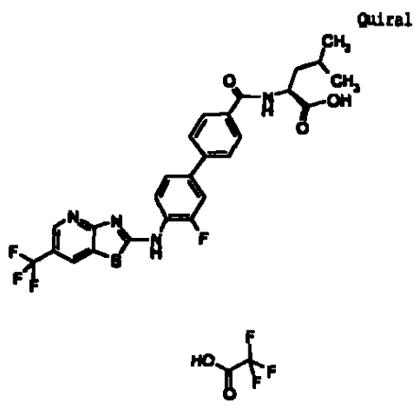
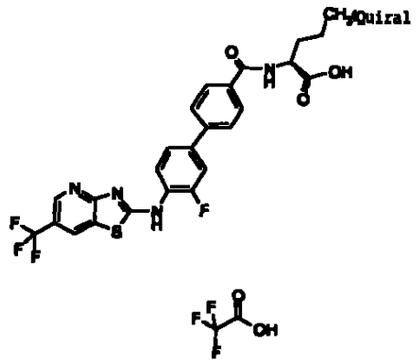
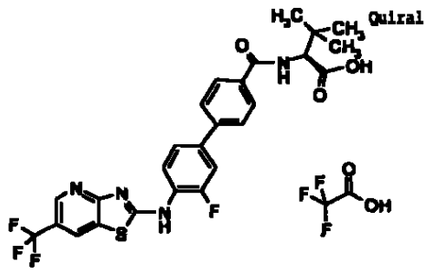
262

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
182		3.87	520.2	A
183		3.77	518.2	A
184		3.37	529.2	A
185		3.23	515.2	A

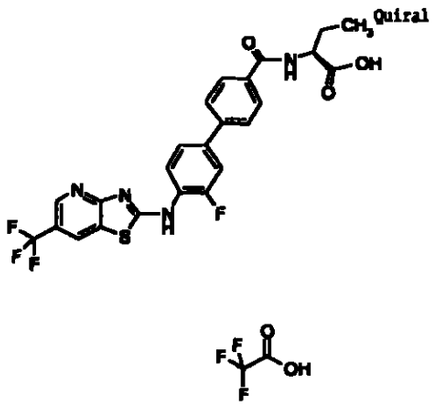
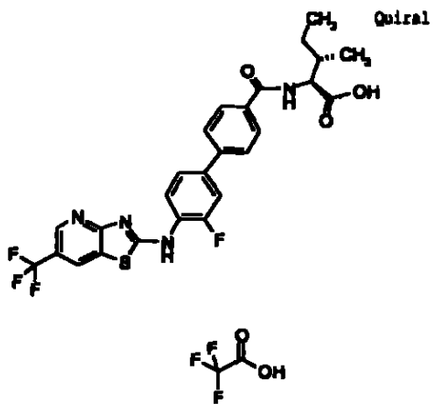
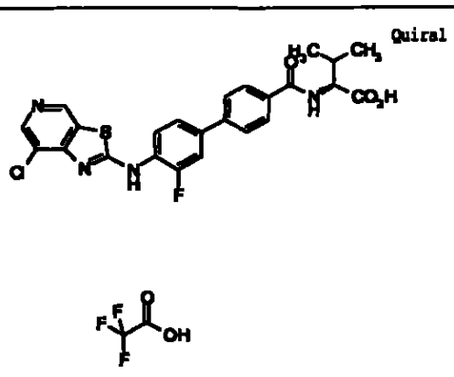
263

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
186		3.35	529.2	A
187		3.11	501.2	A
188		3.35	529.2	A
189		3.25	527.2	A

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Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
190	 Quiral	3.43	547.2	A
191	 Quiral	3.3	533.2	A
192	 Quiral	3.4	547.2	A

205

Ejemplo No.	Estructura	CL-EM Tpo. Ret. (min)	CL-EM [M+H]+	Método
193		3.17	519.2	A
194		3.42	547.2	A
195		2.7	499.1	C

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Tabla 7b. Nombres de IUPAC de Compuestos en Tabla 7a

Ejemplo No.	Nombres de IUPAC
100	N-({4'-[(6-Fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L- alotreonina
101	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-alotreonina
102	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-treonina
103	N-({4'-[(6-Fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L- treonina
104	N-({4'-[(6-Fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L- serina
105	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-O-metil-L-serina
106	3-Ciclopropil-N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2- il)amino]bifenil-4-il}carbonil)-L-alanina
107	N-({4'-[(6-Fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)- O-metil-L-serina
108	3-Ciclopropil-N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil- il}carbonil)-L-alanina 4-
109	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-N-metil-L-valina
110	N-({4'-[(6-Fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)- N-metil-L-valina
111	N-({3-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-valina
112	N-({3-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-leucina
113	N-({3-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-3-metil-L-valina
114	N-({3-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-isoleucina
115	N-({3-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-norvalina
116	Acido (2S)-2-[({3-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil 4.il}carbonil)amino]butanoico
117	3-Ciclopropil-N-({3-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina
118	N-({3,3'-Difluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-valina
119	N-({3,3'-Difluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-L-leucina
120	N-({3,3'-Difluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)-3-metil-L-valina

Ejemplo No.	Nombres de IUPAC
121	N-({3,3'-Difluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-norvalina
122	Acido(2S)-2-[({3,3'-Difluoro-4'-[(6-fluoro-1,3-benzo-tiazol-2-il)amino]bifenil-4-il}carbonil)amino]butanoico
123	3-Ciclopropil-N-({3,3'-difluoro-4'-[(6-fluoro-1,3-ben-zotiazol-2-il)amino]biofenil-4-il}carbonil)-L-alanina
124	N-[(3'-Fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-valina
125	N-[(3'-Fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-ilamino}bifenil-4-il)carbonil-L-leucina
126	N-[(3'-Fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-norvalina
127	N-[(3'-Fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-isoleucina
128	N-[(3'-Fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino,bifenil-4-il)carbonil]-3-metil-L-valina
129	3-Ciclopropil-N-[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-alanina
130	Acido (2S)-2-{[(3'-Fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2- il]amino}bifenil-4-il)carbonil]amino} butanoico
131	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluorobifenil-4-il}carbonil)-L-leucina
132	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)- L-valina
133	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)- L-leucina
134	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)- L-norvalina
135	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)- L-isoleucina
136	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-3- metil-L-valina
137	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluorobifenil-4-il}carbonil)-L-valina
138	N-({4'-[‘6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluorobifenil-4-il}carbonil)-L-norvalina
139	Acido (2S)-2-[({4'-[(6-cloro-1,3-benzotiazol-2-il)ami-no]-3'-fluorobifenil-4-il}carbonil)amino]butanoico
140	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-3- ciclopropil-L-alanina
141	N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluorobifenil-4-il}carbonil)-3-metil-L-valina
142	Acido (2S)-2-[({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)amino]butanoico
143	Trifluoroacetato de N-{[4'-([1,3]tiazolo[5,4-b]piridin-2-ilamino)bifenil-4-il]carbonil}-L- valina

Ejemplo No.	Nombres de IUPAC
144	Trifluoroacetato N-{[4'-({1,3]tiazolo[4,5-c]piridin-2-ilamino)bifenil-4-il]carbonil}-L- valina
145	Trifluoroacetato N-{[4'-({1,3]tiazolo[4,5-b]piridin-2-ilamino)bifenil-4-il]carbonil}-L- valina
146	Trifluoroacetato N-[(3'-Fluoro-4'-{[6-(trifluorometil)[1,3] tiazolo[4,5-b]piridin-2- il]amino}bifenil-4-il)carbonil]-L-valina
147	Trifluoroacetato N-{[3'-Fluoro-4'-([1,3]tiazolo[4,5-c]piridin-2-ilamino)bifenil-4- illcarbonil}-L-valina
148	Trifluoroacetato N-{[3'-Fluoro-4'-([1,3]tiazolo[4,5-b]piridin-2-ilamino)bifenil-4- il]carbonil}-L-valina
149	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-O-metil-L-alotreonina
150	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-N-metil-L-norvalina
151	Acido 4,4,4-Trifluoro-2-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]butanoico
152	N-({3'-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-4-metileno-L-norvalina
153	3-Ciclobutil-N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina
154	Acido (2S)-[({3'-Fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino] bifenil-4-il}carbonil)amino](fenil)acético
I55	N-({4'-[(6-Fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-O-metil-L-alotreonina
156	N-({4'-[(6-Fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-N-metil-L-norvalina
157	Acido 1-[({4'-[(6-Fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)(metil)amino]ciclopropancarboxílico
158	Acido (4R)-3-({4'-[(6-Fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-5,5-dimetil-1,3-tiazolidina-4-carboxílico
159	Acido 4,4,4-Trifluoro-2-[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4- il}carbonil)amino]butanoico
160	N-({4'-[(6-Fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-4-metileno-L-norvalina
161	3-Ciclobutil-N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina
162	Acido (2S)-[({4'-[(6-Fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino](fenil)acético
163	N-[(3'-Fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-valina
164	N-[(3'-Fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-leucina
165	N-[(3'-Fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-norvalina

Ejemplo No.	Nombres de IUPAC
166	N-[(3'-Fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-3-metil-L-valina
167	Acido (2S)-2-{[(3'-Fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]amino}butanoico
168	N-[(3'-Fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-isoleucina
169	3-Ciclopropil-N-[(3'-fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2- il]amino}bifenil-4-il)carbonil]-L-alanina
170	N-((4'-{(6-(Trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-valina
171	N-[(4'-{[6-(Trifluorometil)-1,3-benzotiazol-2-i]]amino}bifenil]-4-il)carbonil]-L-leucina
172	N-[(4'-{[6-(Trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carboni]]-L-norvalina
173	3-Metil-N-[(4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-valina
174	Acido (2S)-2-{[(4'-{[6-(Trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-i])carbonil]amino}butanoico
175	N-[(4'-{[6-(Trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-isoleucina
176	3-Ciclopropil-N-[(4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-alanina
177	N-({3'-Fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina
178	N-({3'-Fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-leucina
179	N-({3'-Fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-norvalina
180	Acido (2S)-2-[({3'-Fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]butanoico
181	N-({3'-Fluoro-4'-[(6-isopropil-],3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-3-metil-L-valina
182	N-({3'-Fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-isoleucina
183	3-Ciclopropil-N-({3'-fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-i])amino]bifenil-4-il}carbonil)-L-alanina
184	Trifluoroacetato N-[(4'-{[6-(Trifluorometil)[1,3]tiazolo[4,5-b]piridin-2- il]amino}bifenil-4-il)carbonil]-L-leucina
185	Trifluoroacetato de N-[(4'-{[6-(Trifluorometil)[1,3]tiazolo[4,5-b]piridin-2- il]amino}bifenil-4-il)carbonil]-L-norvalina

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Ejemplo No.	Nombres de IUPAC
185	Trifluoroacetato de N-[(4'-{[6-(Trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil]-L-norvalina
186	Trifluoroacetato de 3-Metil-N-((4'-{(6-(trifluorometil)[1,3]tiazolo(4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil]-L-valina
187	Trifluoroacetato de ácido (2S)-2-{[(4'-{[6-(Trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil]amino}butanoico
188	Trifluoroacetato de N-[(4'-{[6-(Trifluorometil)[],3]tiazolo[4,5-b]piridin-2- il]amino}bifenil-4-il)carbonil]-L-isoleucina
189	Trifluoroacetato de 3-Ciclopropil-N-((4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2- il]amino}bifenil-4-il)carbonil]-L-alanina
190	Trifluoroacetato de N-((3'-Fluoro-4'-{(6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2- il]amino}bifenil-4-il)carbonil]-L-leucina
191	Trifluoroacetato de N-[(3'-Fluoro-4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2- il]amino}bifenil-4-il)carbonil]-L-norvalina
192	Trifluoroacetato de N-[(3'-Fluoro-4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2- il]amino}bifenil-4-il)carbonil]-3-metil-L-valina
193	Trifluoroacetato de ácido (2S)-2-{[(3'-Fluoro-4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifeni]-4-il)carbonil]amino}butanoico
194	Trifluoroacetato de N-((3'-Fluoro-4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil]-L-isoleucina
195	Trifluoroacetato de N-({4'-[(7-cloro[1,3]tiazolo[5,4-c]piridin-2-il)amino]-3'-fluorobifenil-4-il}carbonil)-L-valina

Métodos de Uso

Como se usa en la presente, en seguida se definen varios términos.

Cuando se introducen elementos de la presente invención o las modalidades preferidas de la misma, los artículos "un", "el" y "dicho" se pretende que sean uno o más elementos. Los términos "que comprenden", "que incluyen"

y "que tienen" se pretenden que sean inclusivos y significan que pueden ser elementos adicionales diferentes a los elementos listados.

El término "sujeto" como se usa en la presente incluye mamíferos (v.gr., seres humanos y animales).

El término "tratamiento" incluye cualquier proceso, acción, aplicación, terapia o similares, en donde a un sujeto que incluye a un ser humano, se le proporciona ayuda médica con el objetivo de mejorar la condición del sujeto, directa o indirectamente, o disminuir la progresión de una condición o trastorno en el sujeto.

El término "terapia de combinación" o "co-terapia" significa la administración de dos o más agentes terapéuticos para tratar una enfermedad, condición /u otro trastorno. Dicha administración abarco la co-administración de dos o más agentes terapéuticos en una forma sustancialmente simultánea, tal como en una sola cápsula que tiene una relación física de ingredientes activos o en múltiples cápsulas separadas para cada agente inhibidor. Además, dicha administración abarca el uso de cada tipo de agente terapéutico en una forma secuencial.

La frase "terapéuticamente efectiva" significa la cantidad de cada agente administrado que logrará la meta de mejorar en una severidad de enfermedad, condición y/o trastorno, mientras que evita o reduce al mínimo efectos

laterales adversos asociados con el tratamiento terapéutico dado.

El término "farmaceuticamente aceptable" significa que el artículo al que se refiere es apropiado para usarse en un producto farmacéutico.

Se espera que los compuestos de la Fórmula (I) de esta invención se valoren como agentes terapéuticos. Consecuentemente, una modalidad de esta invención incluye un método para tratar las diferentes condiciones en un paciente (incluyendo mamíferos) que comprenden administrar a dicho paciente una composición que contienen una cantidad del compuesto de la Fórmula (I) que es efectiva para tratar la condición blanco.

Esta invención se refiere a compuestos que pueden ser útiles para la regulación de consumo alimenticio (v.gr., estimulación y supresión). Por ejemplo, un objeto de esta invención es proveer métodos para tratar obesidad e inducir pérdida de peso en un individuo por administración de un compuesto de la invención. E método de la invención comprende administrar a un individuo una cantidad terapéuticamente efectiva de por lo menos un compuesto de la invención o un profármaco de los mismos, que es suficiente para inducir pérdida de peso. La invención además comprende un método para prevenir ganancia de peso en un individuo administrando una cantidad de por lo menos un compuesto de la invención, o un

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profármaco del mismo, que es suficiente para prevenir ganancia de peso.

La presente invención se refiere al uso de los compuestos de esta invención para el tratamiento de enfermedades relacionadas con enfermedad incluyendo dislipidemia asociada y otras complicaciones relacionadas con obesidad y sobrepeso tales como, por ejemplo, cálculos biliares por colesterol, enfermedad de la vesícula biliar, gota, cáncer (v.gr., colon, recto, próstata, senos, ovario, endometrio, cérvix, vesícula biliar y dicto biliar), anormalidades menstruales, infertilidad, ovarios poliquísticos, osteoartritis y apnea del sueño, así como cierto número de otros usos farmacéuticos asociados con los mismos, tales como al regulación de apetito y consumo de alimentos, dislipidemia, hipertrigliceridemia, Síndrome X, diabetes tipo 2 (diabetes no dependiente de insulita), enfermedades ateroescleróticas tales como falla cardiaca, hierlipidemia, hipercolesteremia, bajos niveles de HDL, hipertensión, enfermedad cardiovascular (incluyendo aterosclerosis, enfermedad cardiaca coronaria, enfermedad de arterias coronarias e hipertensión), enfermedad cerebrovascular tal como apoplejía y enfermedad del vaso periférico. Los compuestos de esta invención también pueden ser útiles para tratar trastornos fisiológicos relacionados con, por ejemplo, regulación de sensibilidad a la insulina,

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respuesta inflamatoria, triglicéridos de plasma, HDL, LDL y niveles de colesterol y similares.

Los compuestos de la Fórmula (I) pueden administrarse solos o en combinación con uno o más agentes terapéuticos adicionales. La terapia por combinación incluye administración de una sola formulación de dosis farmacéutica que contiene un compuesto de la Fórmula (I) y uno o más agentes terapéuticos adicionales, así como la administración del compuesto de la Fórmula (I) y cada uno de los agentes terapéuticos adicionales en su propia formulación de dosis farmacéutica separada. Por ejemplo, un compuesto de la Fórmula (I) y un agente terapéutico puede administrarse al paciente junto con una sola composición de dosis oral tal como una tableta o cápsula, o cada agente puede administrarse en formulaciones de dosis orales separadas.

Cuando se usan las formulaciones de dosis separadas, un compuesto de la Fórmula (I) y uno o más agentes terapéuticos adicionales pueden administrarse esencialmente al mismo tiempo (v.gr., concurrentemente) o en tiempos accionados por separado (v.gr., secuencialmente).

Por ejemplo, un compuesto de la Fórmula (I) puede usarse en combinación con otras terapias y fármacos útiles para el tratamiento de obesidad. Por ejemplo, los fármacos anti-obesidad incluyen agonistas receptores adrenérgicos β-3 tales como CL 316,243; antagonistas canabinoides (v.gr., CB-

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1) tales como Rimonabant; antagonistas del receptor de neuropéptidos Y; inhibidores de neuropéptidos Y5; inhibidores de apo-B/MTP; inhibidores de deshidrogenasa-1 11-β-hidroxi esteroidal; péptido YY_{3-36} o análogos de los mismos: agonistas de MCR4; agonistas de CCK-A; inhibidores de reabsorción de monoamina; agentes simpatomiméticos; agonistas de dopamina; análogos del receptor de hormona estimuladora de melanocitos; antagonistas de hormona de concentración de melanina; leptina; análogos de leptina; agonistas de receptores de leptina; antagonistas de galanina; inhibidores de lipasa; agonistas de bombesina; agentes tiromiméticos; deshidroepiandrosesterona o análogos de los mismos; antagonistas de receptores de glucocorticoides; antagonistas de receptores de orexina; factor neurotófico ciliar; antagonistas de receptores de ghrelina; antagonistas de receptores de histamina-3; agonistas de receptor de neuromedina U; supresores de apetito, tales como, por ejemplo, sibutramina (Meridia); e inhibidores de lipasa, tales como, por ejemplo, orlistat (Xeniçal). Los compuestos de la presente invención también se pueden administrar en combinación con un compuesto de fármaco que modula digestión y/o metabolismo tales como fármacos que modulan termogénesis, lipólisis; movilidad del intestino, absorción de grasas, y saciedad.

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Además de un compuesto de la Fórmula (I) puede administrarse en combinación con uno o más de los siguientes agentes para el tratamiento de diabetes o trastornos relacionados con diabetes incluyendo ligandos de PPAR (agonistas, antagonistas), secretagogos de insulina, sensibilizadores de insulina, compuestos de disminución de salida de glucosa hepática, e insulina y derivados de insulina. Dichas terapias se pueden administrar antes de, concurrentemente con, o después de administración de los compuestos de la invención. La insulina y derivados de insulina incluyen formas de acción tanto larga como corta y formulaciones de insulina. Los ligandos de PPAR pueden incluir agonistas y/o antagonistas de cualquiera de los receptores de PPAR o combinaciones de los mismos. Por ejemplo, los ligandos de PPAR pueden incluir ligandos de PPAR-α, PPAR-γ, PPAR-δ o cualquier combinación de dos o tres de los receptores de PPAR. Los ligandos de PPAR incluyen, por ejemplo, rosiglitazona, troglitazona y pioglitazona. Los fármacos de sulfonilurea incluyen, por ejemplo, gliburido, glimerpirido, clopropanida, tolbutamida, y glipizida. Los inhibidores de α-glucosidasa que pueden ser útiles para tratar diabetes cuando se administra con un compuesto de la invención incluyen acarbosa, miglitol, y boglibosa. Los sensibilizadores de insulina que pueden ser útiles para tratar diabetes incluyen agonistas de PPAR- γ tales como

glitazonas (v.gr., troglitazona, pioglitazona, englitazona, MCC-555, rosiglitazona y similares) y otros compuestos de tiazolidinodiona y sin tiazolidinodiona, biguanidas tales como metformina y fenformina; inhibidores de proteína tirosina fosfatasa-1B (PTP-1B); inhibidores de dipeptidil peptidasa IV (DPP-IV), e inhibidores 11 beta-HSD. Los compuestos de disminución de salida de glucosa hepática que pueden ser útiles para tratar diabetes cuando se administran con un compuesto de la invención incluyen antagonistas de glucagon y metformina, tales como Glucofago y Glucofago XR. Los secretagogos de insulina que pueden ser útiles para tratar diabetes cuando se administran con un compuesto de la invención incluyen fármacos de sulfonilurea y que no son sulfonilurea: GLP-1, GIP, PACAP, secretina, y derivados de la misma; nateglinida, meglitinida, repaglinida, glibenclamida, glimepirida, clopropamida, glipzida. GLP-1 incluye derivados de GLP-1 con vidas medias más largas que GLP-1 nativos, tales como, por ejemplo GLP-1 derivatizados de ácidos grasos y exendina.

Los compuestos de la invención también se pueden usar en métodos de la invención en combinación con fármacos usados comúnmente para tratar trastornos de lípidos en pacientes. Dichos fármacos incluyen, pero no están limitados a inhibidores de HMG-CoA reductasa, ácido nicotínico, compuestos de disminución de ácido graso (v.gr., acipimox);

fármacos de disminución de lípidos (v.gr., ésteres de estanol, esterol glucósidos tales como tiquesida y azetidinonas tales como ezetimibe), inhibidores de ACAT (tales como avasimibe) secuestradores de ácido biliar, inhibidores de reabsorción de ácido biliar, inhibidores de transporte de triglicéridos microsomales y derivados de ácido fíbrico. Los inhibidores de HMG-CoA reductasa incluyen, por ejemplo, lovastatina, simvastatina, pravastatina, fluvastatina, atorvastatina, rivastatina, itavastatina, cerivastatina y ZD-4522. Los derivados de ácido fíbrico incluyen, por ejemplo, clofibrato, fenofibrato, benzafibrato, ciprofibrato, beclofibrato, etofibrato y gemfibrozilo. Los secuestradores incluyen, por ejemplo colestiramina, colestipol, y derivados de dialquilaminoaquilo de un dextrano entrelazado.

Los compuestos de la invención también se pueden usar en combinación con fármacos anti-hipertensivos, tales como, por ejemplo, bloqueadores β, e inhibidores de ACE. Ejemplos de agentes anti-hipertensivos adicionales para usarse en combinación con los compuestos de la presente invención incluyen bloqueadores de canal de calcio (Tipo L y tipo T; v.gr., diltiazem, verapamil, nifedipina, amlodipina y mibefradilo), diuréticos (v.gr., clorotiazida, hidroclorotiazida, flumetiaida, hidroflumetiazida, bendroflumetiazida, metilclorotiazida, triclorometiazida,

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politiazida, benztiazida, ácido etacrínico tricrinafeno, clotalidona, furosemida, musolimina, bumetanida, triamtreneno, amilorudo, espironolactona), inhibidores de renina, inhibidores de ACE (v.gr., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), antagonistas de receptores de AT-1 (v.gr., losartan, irbesartan, valsartan), antagonistas de receptor de ET (v.gr., sitaxsentan, atrsentan, inhibidores de endopeptidasa neutral (NEP), inhibidores de vasopepsidasa (inhibidores de NEP-ACE doble) (v.gr., omapatrilat y gemopatrilat) y nitratos.

Los compuestos de la Fórmula (I) también se pueden utilizar, en forma de base libre o en composiciones, así como en investigación y diagnósticos o como estándares de referencia analítica, y similares, que son bien conocidos en la materia. Por lo tanto, la presente invención incluye composiciones que están comprendidas de un vehículo inerte y una cantidad efectiva de un compuesto de la Fórmula (I), o una sal, o éster del mismo. Un vehículo inerte es cualquier material que no interactúa con el compuesto que será portado y que da soporte, medios de transporte, volumen material rastreable y similares al compuesto que será portado. Una cantidad efectiva del compuesto es la cantidad que produce un resultado ejerce una influencia en el procedimiento particular que se está llevando a cabo.

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Se anticipa que se probará que las formas de profármaco de esta invención son útiles en ciertas circunstancias, y dichos compuestos también se pretende que estén dentro del alcance de la invención. Las formas de profármaco pueden tener ventajas sobre los compuestos madre ejemplificados en la presente, dado que son mejor absorbidos, mejor distribuidos, penetran más fácilmente al sistema nervioso centra, son metabolizados o eliminados más lentamente, etc. Las formas de profármacos también pueden tener ventajas en la formulación en términos de cristalinidad o solubilidad de agua. Por ejemplo, los compuestos de la invención que tienen uno o más grupos hidroxilo pueden convertirse a ésteres o carbonatos que tienen uno o más grupos carbonilo, hidroxilo o amino, que se hidrolizan a valores de pH fisiológicos o se separan por esterasas o lipasas endógenas *in vivo* (ver, por ejemplo, las Patentes de E.U.A. Nos. 4,942,184; 4,960,790; 5,817,840; y 5,824,701, todas las cuales se incorporan aquí por referencia en su totalidad y referencias en las mismas).

Composiciones Farmacéuticas

Con base en las pruebas anteriores, u otros análisis conocidos usados para determinar la eficacia para el tratamiento de condiciones identificadas antes en mamíferos o

por comparación de estos resultados con los resultados de medicamentos conocidos que se usan para tratar estas condiciones, la dosis efectiva de los compuestos de esta invención pueden determinarse fácilmente para tratamiento de cada indicación deseada. La cantidad del ingrediente activo que será administrado en el tratamiento de cada indicación deseada. La cantidad del ingrediente activo que será administrado en el tratamiento de una o estas condiciones puede variar ampliamente de acuerdo con dichas consideraciones que el compuesto particular y dosis unitaria empleada, el modo de administración, el periodo de tratamiento, la edad y sexo del paciente tratado y la naturaleza y grado de la condición tratada.

La cantidad total del ingrediente activo que será administrado, por lo general, puede variar generalmente, por ejemplo, de aproximadamente 0.001 mg/kg a alrededor de 200 mg/kg. Una dosis unitaria puede contener de aproximadamente, por ejemplo, de alrededor de 0.05 mg a alrededor de 1500 mg de ingrediente activo, y se puede administrar una o mas veces por día. La dosis diaria para administración por inyección, incluyendo inyecciones intravenosas, intramusculares, subcutáneas y parenterales, y el uso de técnicas de infusión pueden se, por ejemplo, de aproximadamente 0.01 a alrededor de 200 mg/kg. El régimen de dosis rectal diario puede ser, por ejemplo, de 0.01 a 200 mg/kg de peso corporal total. La

concentración transdérmica puede ser la requerida para mantener una dosis diaria, por ejemplo, de 0.01 a 200 mg/kg.

Desde luego, el régimen de dosis inicial y continua específica para cada paciente variará de acuerdo con la naturaleza y severidad de la condición como se determinó por quien diagnostica, la actividad del compuesto específico empleado, la edad del paciente, la dieta del paciente, el tiempo de administración, ruta de administración, régimen de excreción del fármaco, combinaciones de fármacos y similares. El modo deseado de tratamiento y número de dosis de un compuesto de la presente invención o una sal farmacéuticamente aceptable del mismo puede asegurarse por los expertos en la materia usando pruebas de tratamiento convencional.

Los compuestos de esta invención se pueden utilizar para lograr el efecto farmacológico deseado por administración a un sujeto que necesita el mismo en una composición farmacéutica formulada de manera apropiada. Un sujeto, por ejemplo, puede ser un mamífero, incluyendo un ser humano, que necesita el tratamiento para una condición o enfermedad particular. Por lo tanto, la presente invención incluye composiciones farmacéuticas que están comprendidas de un vehículo farmacéuticamente aceptable y una cantidad farmacéuticamente efectiva de un compuesto identificado por los métodos descritos en la presente, o una sal o éster

farmacéuticamente aceptable del mismo. Un vehículo farmacéuticamente aceptable es cualquier vehículo que es relativamente no tóxico e inocuo a un paciente a concentraciones consistentes con actividad efectiva del ingrediente activo de manera que los efectos laterales que se le atribuyen al portador sin viciar los efectos benéficos del ingrediente activo. Una cantidad farmacéuticamente efectiva de un compuesto es que la cantidad que produce un resultado o ejerce e influencia la condición particular que está siendo tratada. Los compuestos identificados por los métodos descritos en la presente pueden administrarse con un vehículo farmacéuticamente aceptable usando cualquier forma de dosis unitaria convencional efectiva, incluyendo, por ejemplo, preparaciones de liberación inmediata y de tiempo controlado, oralmente, parenteralmente, tópicamente o similares.

Para administración oral, los compuestos pueden formularse en preparaciones sólidas o líquidas tales como, por ejemplo, cápsulas, píldoras, tabletas, trociscos, pastillas, mezclas, polvos, soluciones, suspensiones o emulsiones y pueden prepararse de acuerdo con métodos conocidos en la materia para la manufactura de composiciones farmacéuticas. Las formas de dosis unitarias sólidas pueden ser una cápsula que puede ser del tipo de gelatina suave o dura cubierta común que contiene, por ejemplo, agentes

tensioactivos, lubricantes, y rellenos inertes tales como lactosa, sacarosa, fosfato de calcio y almidón de maíz.

En otra modalidad, los compuestos de esta invención pueden ser tabletas con bases de tabletas convencionales tales como lactosa, sacarosa y almidón de maíz en combinación con aglutinantes tales como acacia, almidón de maíz o gelatina; agentes desintegrantes que se pretende que ayuden a romper y disolver la tableta después de la administración tal como almidón de papa, ácido algínico, almidón de maíz y goma guar; lubricantes que se pretende que mejoren el flujo de granulación de tabletas y para prevenir la adhesión de material de tabletas a las superficies de los colorantes y perforadores de tabletas, por ejemplo, talco, ácido esteárico o estearato de magnesio, calcio o zinc; tintes, agentes colorantes; y agentes saborizantes que se pretende que mejoren las calidades estéticas de las tabletas y las hace más aceptables por el paciente. Los excipientes adecuados para usarse en formas de dosis líquidas orales incluyen diluyentes tales como agua y alcoholes, por ejemplo, etanol, alcohol bencílico y alcoholes de polietileno, ya sea cono sin la adición de un agente tensioactivo farmacéuticamente aceptable, agente de suspensión o agente emulsificante. Otros diferentes materiales pueden estar presentes como revestimientos o de alguna manera modificar la forma física

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de la dosis unitaria. Por ejemplo, tabletas, píldoras o cápsulas pueden revestirse con laca, azúcar o ambas.

Los polvos y gránulos dispersibles son adecuados para la preparación de una suspensión acuosa. Proveen el ingrediente activo en mezcla con un agente dispersante o humectante, un agente de suspensión, y uno o más conservadores. Los agentes dispersantes o humectantes adecuados y agentes de suspensión se ejemplifican por los ya mencionados antes. Los excipientes adicionales, por ejemplo, pueden estar presentes los agentes edulcorantes, saborizantes y colorantes descritos antes.

Las composiciones farmacéuticas de esta invención también pueden tener la forma de emulsiones de aceite en agua. La fase oleosa puede ser un aceite vegetal tal como parafina líquida o una mezcla de aceites vegetales. Los agentes emulsificantes adecuados pueden ser (1) gomas presentes en la naturaleza tales como goma de acacia y goma de tragacanto, (2) fosfatidos presentes en la naturaleza tales como soya y lecitina, (3) esteres o esteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de sorbitán, y (4) productos de condensación de dichos ésteres parciales con óxido de etileno, por ejemplo, monooleato de polioxietileno sorbitán. Las emulsiones también pueden contener agentes edulcorantes y saborizantes.

Los jarabes y elíxires pueden formularse con agentes edulcorantes tales como, por ejemplo, glicerol, propilenglicol, sorbitol, o sacarosa. Dichas formulaciones también pueden contener un demulcente, y agentes conservadores, saborizantes y colorantes.

Los compuestos de esta invención también se pueden administrar parenteralmente, es decir, subcutáneamente, intravenosamente, intramuscularmente, o intraperitonealmente, como dosis inyectables del compuesto en un diluyente fisiológicamente aceptable con un vehiculo farmacéutico que puede ser un líquido estéril o mezcla de líquidos tales como agua, solución salina, dextrosa acuosa y soluciones de azúcares relacionadas; un alcohol; glicoles; glicerol cetales, éteres; un aceite; un ácido graso; un éster de ácido graso o glicérido; o un glicérido de ácidos grasos acetilado con o sin la adición de un agente tensioactivo farmacéuticamente aceptable; agente de suspensión; o agente emulsificante y otros adyuvantes farmacéuticos.

Las composiciones parenterales de esta invención pueden contener normalmente de aproximadamente 0.5% a alrededor de 25% en peso del ingrediente activo en solución. Los conservadores y reguladores de pH también se pueden usar ventajosamente. Con el fin de reducir al mínimo o eliminar la irritación en el sitio de inyección, dichas composiciones pueden contener un agente tensioactivo no iónico que tiene un

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balance hidrofílico-lipofílico (HLB) de aproximadamente 12 a alrededor de 17. La cantidad de agente tensioactivo en dicha formulación varía de aproximadamente 5% a alrededor de 15% en peso. El agente tensioactivo puede ser un solo componente que tiene el HLB anterior o puede ser una mezcla de dos o más componentes que tienen el HLB deseado.

Las composiciones farmacéuticas pueden tener la forma de suspensiones acuosas inyectables estériles. Dichas suspensiones pueden formularse de cuerdo con métodos conocidos usando agentes dispersantes o humectantes adecuados y agentes de suspensión, agentes de dispersión o humectación que pueden ser fosfatidos presentes en la naturaleza, un producto de condensación de un óxido de alquileno con un pacido graso, un producto de condensación de óxido de etileno con n alcohol alifático de cadena larga, un producto de condensación de óxido de etileno con un éster parcial derivado de un ácido graso y un hexitol, o un producto de condensación de un óxido de etileno con un éster parcial derivado de un ácido graso y un anhídrido de hexitol.

La preparación inyectable estéril también puede ser una solución o suspensión inyectable estéril o un diluyente o solvente no tóxico parenteralmente aceptable. Los diluyentes y solventes que pueden emplearse son, por ejemplo, agua, solución de Ringer, y solución de cloruro de sodio isotónica. Además, los aceites fijos estériles se emplean

convencionalmente como solventes o medios de suspensión. Con este fin, se puede emplear cualquier aceite fijo suave incluyendo mono o diglicéridos sintéticos. Además, los ácidos grasos tales como ácido oleico pueden usarse en la preparación de inyectables.

Una composición de la invención también se puede administrar en forma de supositorios para administración rectal del fármaco. Estas composiciones pueden prepararse mezclando el fármaco con un excipiente sin irritación adecuado que es sólido a temperaturas ordinarias pero es líquido a la temperatura rectal y por lo tanto se fundirá en el recto para liberar el fármaco. Dicho material, por ejemplo, puede ser manteca da cacao y polietilenglicol.

Otra formulación empleada en los métodos de al presente invención emplea dispositivos de suministro transdérmicos ("parches"). Dichos parches transdérmicos se pueden usar para proveer infusión continua o discontinua de los compuestos de la presente invención en cantidades controladas. La construcción y uso de parches transdérmicos para el suministro o agentes farmacéuticos es bien conocido en la materia (véase, v.gr., Patente de E.U.A. No. 5,023,252, incorporada aquí por referencia). Dichos parches pueden construirse para suministro continuo, pulsátil bajo demanda de agentes farmacéuticos.

Puede ser conveniente o necesario introducir la composición farmacéutica al paciente vía un dispositivo de suministro mecánico. La construcción y uso de dispositivos de suministro mecánico para el suministro de agentes farmacéuticos es bien conocido en la materia. Por ejemplo, las técnicas directas para administrar un fármaco directamente al cerebro implica usualmente la colocación de un catéter de suministro de fármaco en el sistema ventricular del paciente para derivar la barrera de fuga sanguínea. Uno de dichos sistemas de suministro implantable usado para el transporte de agentes a regiones anatómicas específicas del cuerpo, se describió en la Patente de E.U.A. No. 5,011,472, incorporada aquí por referencia.

Otra formulación emplea el uso de microesferas biodegradables que permiten liberación sostenida controlada. Dichas formulaciones pueden estar comprendidas de polímeros o copolímeros sintéticos. Dichas formulaciones permiten inyección, inhalación, administración nasal u oral. La construcción y uso de microesferas biodegradables para el suministro de agentes farmacéuticos es bien conocido en la materia (v.gr., Patente de EUA No. 6,706,289, incorporada aquí por referencia).

Las composiciones de la invención también pueden contener otros ingredientes de formación de compuestos farmacéuticamente aceptables convencionales, denominados

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generalmente como vehículos o diluyentes, según sea necesario o deseado. Cualquiera de las composiciones de esta invención puede conservarse por la adición de un antioxidante tal como ácido ascórbico o por otros conservadores adecuados. Se pueden utilizar procedimientos convencionales para preparar dichas composiciones en formas de dosis apropiadas.

Los compuestos identificados por los métodos descritos en la presente se pueden administrar como el único agente farmacéutico o en combinación con uno o más agentes farmacéuticos en donde la combinación no ocasiona efectos adversos inaceptables. Por ejemplo, los compuestos de esta invención se pueden combinar con anti-obesidad conocida, o con agentes u otra indicación conocidos y similares, así como con mezclas y combinaciones de los mismos.

Los compuestos identificados por loes métodos descritos en la presente se pueden utilizar, en forma de base libre o en composiciones, en investigación y diagnóstico o como estándares de referencia analítica, y similares. Por lo tanto, la presente invención incluye composiciones que están comprendidos de un vehículo inerte y una cantidad efectiva de un compuesto identificado por los métodos descritos en la presente, o una sal o éster del mismo. Un vehículo inerte es cualquier material que no interactúa con el compuesto para ser portado y que da soporte, medios de transporte, volumen, material rastreable y similares al compuesto que será

transportado. Una cantidad efectiva del compuesto es esa cantidad que produce un resultado o ejerce una influencia en el procedimiento particular que se está realizando.

Las formulaciones adecuadas para administración subcutánea, intravenosa, intramuscular y similares; vehículos farmacéuticos adecuados; y técnicas para formulación y administración peden prepararse por cualquiera de los métodos bien conocidos en la materia (véase, v.gr., Remington's Pharmaceutical Sciences, Mack Publishing Col., Easton, PA., 20a. edición, 2000).

Las estructuras, materiales, composiciones y métodos descritos en la presente se pretende que sean ejemplos representativos de la invención y se entenderá que el alcance de la invención no se limita por el alcance de los ejemplos. Los expertos en la materia reconocerán que la invención puede practicarse con variaciones en las estructuras, materiales, composiciones y métodos descritos, y dichas variaciones se consideran dentro del ámbito de la invención.

ACTIVIDAD BIOLÓGICA DE LOS COMPUESTOS

Con el fin de que se entienda mejor esta invención, se exhiben los siguientes ejemplos. Estos ejemplos son con el fin de ilustración únicamente, y no se deberán interpretar

como limitantes del alcance de la invención de cualquier manera. Todas las publicaciones mencionadas en la presente se incorporan en su totalidad por referencia.

La demostración de la actividad de los compuestos de la presente invención se puede lograr a través de análisis *in vitro*, *ex vivo* e *in vivo* que son bien conocidos en la materia. Por ejemplo, para demostrar la eficacia de un agente farmacéutico para el tratamiento de obesidad y trastornos relacionados, se pueden usar los siguientes análisis.

Evaluación del Efecto del Compuesto en la Inhibición de la Actividad de la Enzima DGAT-1

El gen de DGAT-1 humano (véase por ejemplo, Patente de E.U.A. No. 6,100,077) se aisló de un banco de ADNc humano por RCP. Se construyó el baculovirus recombinante de AcNPV en el cual se reemplazó el gen para la polihedrina de proteína de formación de cuerpo de oclusión con el gen de DGAT-1. La secuencia del gen de DGAT-1 se insertó en el genoma 3' de AcNPV a la secuencia del promotor de polihedrina colocando DGAT-1 bajo el control transcripcional del promotor de polihedrina. Se infectaron células del insecto Sf9 derivados de Spodoptera frugiperda con baculovirus recombinante conteniendo DGAT-1 en la multiplicidad de infección de 5 y infección posterior a 48 horas recuperado. Las células de

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insectos de expresión de DGAT-1 se homogeneizaron en 10 mM de Tris, 25' mM de sacarosa pH 7.5 a la concentración de 100 mg de biomasa de célula húmeda por ml. El homogenado se centrifugó a 25,000 g durante 30 min. La pella de 25,000 se descartó y el sobrenadante se centrifugó a 25,000 g durante 30 min. La pella de 25,000 g se descartó y los 100,000 g sobrenadante se centrifugaron durante 1 h. El sobrenadante de 100,000 g se descarto y la pella de membrana que contiene 100,000 g de DGAT-1 se resuspendió en 10 mM de Tris, 50% (v/v) de glicerol pH 7.5.

La actividad de la enzima DGAT-1 se determinó por un protocolo de división de fases. Específicamente, se incubaron membranas conteniendo DGAT-1 en 20 mM de didecanoil glicerol, 5 mM ^{14}C-decanoil-CoA, 2 mM $MgCl_2$, 0.01% BSA, 50 mM HEPES, solución reguladora a pH 7.5 en presencia de concentraciones variables de inhibidores. Se realizaron análisis en volúmenes de 100 µl en placas de microtitulación de 96 pozos con 0.5 µg de proteína de membrana total por pozo. El análisis se inició por el sustrato y se mezcló suavemente durante 1 h a temperatura ambiente. La actividad se enfrió por la adición de 25 µl de solución de ácido fosfórico al 0.1%. La extracción selectiva del producto de tridecanoilglicerol hidrofóbico se logró por la adición de fluido de centelleo de división de fases de 150 µl Microscint® (Packard, Inc.) y mezclado vigoroso Durante 30

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min. La cuantificación del producto se logró por un contador de centelleo MicroBeta® (Wallac, Inc.) después de reposo a temperatura ambiente durante aproximadamente 16 h.

Evaluación del Efecto del Compuesto sobre la Inhibición del Depósito de Triglicéridos Celular

El análisis basado en células para DGAT-1 se condujo con células de adenocarcinoma colorectal humano HT-29 (HTB-38, ATCC). Las células de HT-29 se desarrollaron en placa de 75 cm^2 hasta ~90% confluente en medio DMEM con FBS al 10%, PSF, glutamina y acetato 10 mM. Las células se volvieron a sembrar en placas de nuevo en placas de 24 pozos para dar dilución de 1:1.2 y se desarrollaron aproximadamente 16 h. La formación de tiacilglicérido se estimuló por la adición de ácido laurico a una concentración final de 0.01% en presencia de concentraciones variables de inhibidores. Después de 6 h, se liberaron células de la placa por tripsina, se recuperaron por centrifugación, se resuspendieron en agua, se transfirieron a CLAR de vidrio, se congelaron a -70°C y se liofilizaron. Las pellas de células secas congeladas se resuspendieron en 150 µl de tetrahidrofurano de grado de CLAR y se sellaron en frascos viales. Los frascos viales se trataron con sonido durante 30 min con calentamiento en un baño de agua con sonido (Fisher,

Inc.). Los triacilglicéridos celulares se cuantificaron por CLAR (HP 1100, Agilent, Inc.) usando detección de barrido luminoso evaporativo (PL-ELS 1000, Polymer Labs, Inc.). La separación cromatográfica se logró por solución reguladora De pH B de 30 a 100% en 4 minutos seguido por 3 minutos en solución reguladora de pH B a 100% usando una columna de PLRP S 100 (5 micras, 150 x 4.6 mm, Polymer Labs, Inc.) a 50°C (A: 50% acetonitrilo, 2.5% metanol, B: 100% tetrahidrofurano). Las inyecciones de muestras fueron de 20 µl y el detector se fijó a 0.4 SLM, nebulizador a 40°C , y evaporador a 80°C. Los ácidos grasos no polares y lípidos de glicerol se identificaron y cuantificaron usando normas comercialmente disponibles.

Evaluación de Eficacia de Compuestos en la Reducción de Peso Corporal en Ratones Obesos Inducidos por Dieta

El propósito de este protocolo es determinar el efecto de administración crónica de un compuesto en el peso corporal de ratones hechos obesos por exposición a una dieta con alto contenido en grasas de 45% de kcal/g durante más de 10 semanas. El peso corporal de ratones seleccionados para estos estudios fue superior a tres desviaciones estándar del peso de un grupo de control de ratones alimentados con croquetas para ratones normales con bajo contenido de grasas

(5-6% de grasas). Los animales obesos inducidos por dieta (OID) se han usado frecuentemente en la determinación de la eficacia de compuestos en la reducción de peso corporal (véase, por ejemplo, Brown, y otros, Brit. J. Pharmacol. 132: 1898-1904, 2001; Guerre-Millo, y otros, J. Biol. Chem. 275(22): 16638-42, 2000; Han, y otros, Intl. J. Obesity and Related Metabolic Disorders 23(2): 174-79, 1999; Surwit, y otros, Endocrinol. 141(10): 3630-37, 2000).

Este modelo animal se ha usado exitosamente en la identificación y caracterización del perfil de eficacia de compuestos que son o se han usado en el manejo de peso corporal en seres humanos obesos (véase, por ejemplo, Brown, y otros, 2001; Guerre-Millo, y otros, 2000; Han, y otros, 1999).

Un estudio normal incluyó de 60-80 ratones machos C57b1/J6 (m= 10/grupo de tratamiento) con un peso corporal promedio de aproximadamente 45g. Los ratones se mantienen en habitaciones normales para animales bajo temperatura y humedad controladas y un ciclo de iluminación/oscuridad de 12 horas/12 horas. Continuamente se administraron agua y alimento. Los ratones se alojaron individualmente. Los animales se dosificaron simuladamente con vehículo del estudio durante por lo menos cuatro días antes de registrar mediciones de línea de base de dos días del peso corporal y consumo de agua y alimento de 24 horas. Los ratones fueron

asignados a 6-8 grupos de tratamiento con base en su peso corporal en la línea de base. Los grupos se establecieron de manera que la media y el error estándar de la media del peso corporal fueron similares.

Los animales se alimentaron mediante sondas (5 ml/kg) antes de la fase oscura del ciclo iluminado/oscuro durante un número predeterminado de días (normalmente 8-14 días) con su dosis/compuesto asignado. Se midieron peso corporal y consumo de alimento y agua. Los datos se analizaron usando estadística apropiada siguiendo el diseño de investigación. En el último día, se sacrificaron los animales usando inhalación de CO_2.

Los compuestos se dosifican normalmente a 30 mg/kg p.o.q.d., y se consideraron activos los compuestos si se observó una reducción estadísticamente importante para los animales tratados, en relación con animales de control tratados por vehículo.

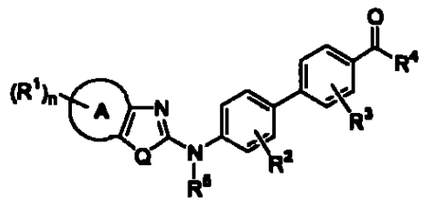
Las estructuras, materiales, composiciones, y métodos descritos en la presente se pretende que sean ejemplos representativos de la invención, y se entenderá que el alcance de la invención no se limite por el alcance de los ejemplos. Los expertos en la materia reconocerán que la invención puede practicarse con variaciones en las estructuras, materiales, composiciones y métodos descritos,

y dichas variaciones se consideran dentro del ámbito de la invención.

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REIVINDICACIONES

1.- Un compuesto de la Fórmula (I)



(I)

en donde

Q es O, NR^{11}, o S;



es un anillo fusionado seleccionado de un anillo aromático de 6 miembros conteniendo 0 ó 1 átomos de N;

R^1 es independientemente seleccionado de halo, alquilo de (C_1-C_6), alcoxi de (C_1-C_6), nitro, ciano, haloalquilo de (C_1-C_6), haloalcoxi de (C_1-C_6), aminocarbonilo, alquilaminocarbonilo de (C_1-C_6), bis{alquilo(C_1-C_6)] aminocarbonilo, aminosulfonilo, alquilaminosulfonilo de (C_1-C_6), bis[alquilo de (C_1-C_6)] aminosulfonilo, alquilcarbonilamino de (C_1-C_6), alquilsulfonilo de (C_1-C_6), alquilsulfonilamino de (C_1-C_6), hidroxi-

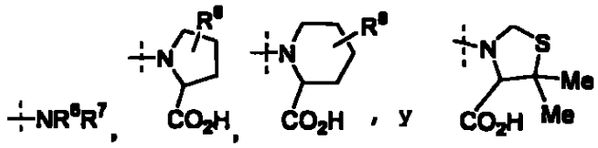
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alquilaminocarbonilo de (C_2-C_6), 1-morfolinilcarbonilo, y 1-piperidinilcarbonilo, y Cuando dos de dichos sustituyentes de R^1 son alquilo de (C_1-C_6), y se unen a átomos de carbono adyacentes del Anillo A, pueden unirse para formar un anillo carbocíclico de 5-7 miembros;

n es 0, 1, ó 2;

R^2 y R^3 se seleccionan independientemente de hidrógeno, halo, hidroxi, alquilo de (C_1-C_6), trifluorometilo, alcoxi de (C_1-C_6), y trifluorometoxi;

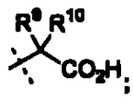
R^4 se selecciona de



en donde:

R^6 es H o CH_3;

y

R^7 es  ;

en donde

R^9 se selecciona de

Alquilo de (C_1-C_6) opcionalmente sustituido con uno o dos grupos seleccionados de vinilo, CF_3, OH, metoxi, SCH_3, NH_2, $-CO_2H$, y $-CONH_2$,

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Fenilo de $(CH_2)_m$ en donde m es de 0 a 3, y

En donde el anillo de fenilo es opcionalmente sustituido con uno o dos grupos seleccionados de halo, alquilo de (C_1-C_6), alcoxi de (C_1-C_6), OH, nitro y ciano,

piperidinilo opcionalmente sustituido en C con halo y opcionalmente sustituido con C o N con alquilo de (C_1-C_6), alcoxi de (C_1-C_6), nitro, o ciano,

tetrahidropiran-4-ilo;

R^{10} es H o metilo;

o

R^9 y R^{10} pueden formar, junto con el carbono al que se unen, un anillo carbocíclico de 3 a 6 miembros,

R^8 es hidrógeno, alquilo de (C_1-C_6), hidroxi o metoxi;

R^5 se selecciona de H, alquilo de (C_1-C_6), e hidroxi-alquilo de (C_2-C_6);

R^{11} se selecciona de H, alquilo de (C_1-C_6), e hidroxi-alquilo de (C_2-C_6);

y sales y ésteres farmacéuticamente aceptables de los mismos.

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2.- El compuesto de la reivindicación 1, en donde

Q es O, NR^{11}, o S;



es un anillo fusionado seleccionado de un anillo aromático de 6 miembros conteniendo 0 ó 1 átomos de N;

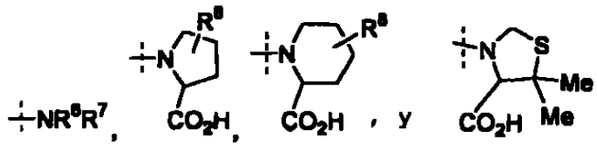
R^1 es independientemente seleccionado de halo, alquilo de (C_1-C_6), alcoxi de (C_1-C_6), nitro, ciano, haloalquilo de (C_1-C_6), haloalcoxi de (C_1-C_6), aminocarbonilo, alquilaminocarbonilo de (C_1-C_6), bis{alquilo(C_1-C_6)] aminocarbonilo, aminosulfonilo, alquilaminosulfonilo de (C_1-C_6), bis[alquilo de (C_1-C_6)] aminosulfonilo, alquilcarbonilamino de (C_1-C_6), alquilsulfonilo de (C_1-C_6), alquilsulfonilamino de (C_1-C_6), hidroxi-alquilaminocarbonilo de (C_2-C_6), 1-morfolinilcarbonilo, y 1-piperidinilcarbonilo, y Cuando dos de dichos sustituyentes de R^1 son alquilo de (C_1-C_6), y se unen a átomos de carbono adyacentes del Anillo A, pueden unirse para formar un anillo carbocíclico de 5-7 miembros;

n es 0, 1, ó 2;

R^2 y R^3 se seleccionan independientemente de hidrógeno, halo, hidroxi, alquilo de (C_1-C_6), trifluorometilo, alcoxi de (C_1-C_6), y trifluorometoxi;

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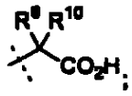
R^4 se selecciona de



en donde:

R^6 es H o CH_3;

y

R^7 es  ;

en donde

R^9 se selecciona de

Alquilo de (C_1-C_6) opcionalmente sustituido con uno o dos grupos seleccionados de vinilo, CF_3, OH, metoxi, SCH_3, NH_2, $-CO_2H$, y $-CONH_2$,

Fenilo de $(CH_2)_m$ en donde m es de 0 a 3, y

En donde el anillo de fenilo es opcionalmente sustituido con uno o dos grupos seleccionados de halo, alquilo de (C_1-C_6), alcoxi de (C_1-C_6), OH, nitro y ciano,

piperidinilo opcionalmente sustituido en C con halo y opcionalmente sustituido con C o N con alquilo de

(C_1-C_6), alcoxi de (C_1-C_6), nitro, o ciano,

tetrahidropiran-4-ilo;

R^{10} es H o metilo;

o

R^9 y R^{10} pueden formar, junto con el carbono al que se unen, un anillo carbocíclico de 3 a 6 miembros,

R^8 es hidrógeno, alquilo de (C_1-C_6), hidroxi o metoxi;

R^5 se selecciona de H, alquilo de (C_1-C_6), e hidroxi-alquilo de (C_1-C_6);

R^{11} se selecciona de H, alquilo de (C_1-C_6), e hidroxi-alquilo de (C_1-C_6).

3.- El compuesto de la reivindicación 1, en donde

Q es O, NR^{11}, o S;



es un anillo fusionado seleccionado de

un anillo aromático de 6 miembros conteniendo 0 ó 1 átomos de N;

R^1 es independientemente seleccionado de halo, alquilo de (C_1-C_6), alcoxi de (C_1-C_6), nitro, ciano, haloalquilo de (C_1-C_6), haloalcoxi de (C_1-C_6), aminocarbonilo, alquilaminocarbonilo de (C_1-C_6), bis[alquilo(C_1-C_6)] aminocarbonilo,

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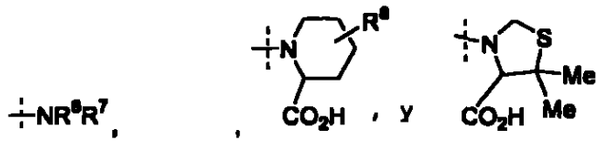
aminosulfonilo, alquilaminosulfonilo de (C_1-C_6), bis[alquilo de (C_1-C_6)] aminosulfonilo, alquilcarbonilamino de (C_1-C_6), alquilsulfonilo de (C_1-C_6), alquilsulfonilamino de (C_1-C_6), hidroxi-alquilaminocarbonilo de (C_2-C_6), 1-morfolinilcarbonilo, y 1-piperidinilcarbonilo, y

Cuando dos de dichos sustituyentes de R^1 son alquilo de (C_1-C_6), y se unen a átomos de carbono adyacentes del Anillo A, pueden unirse para formar un anillo carbocíclico de 5-7 miembros;

n es 0, 1, ó 2;

R^2 y R^3 se seleccionan independientemente de hidrógeno, halo, hidroxi, alquilo de (C_1-C_6), trifluorometilo, alcoxi de (C_1-C_6), y trifluorometoxi;

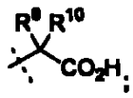
R^4 se selecciona de



en donde:

R^6 es H o CH_3;

y

R^7 es  ;

en donde

R^9 se selecciona de

Alquilo de (C_1-C_6) opcionalmente sustituido con uno o dos grupos seleccionados de vinilo, CF_3, OH, metoxi, SCH_3, NH_2, $-CO_2H$, y $-CONH_2$,

Fenilo de $(CH_2)_m$ en donde m es de 0 a 3, y

En donde el anillo de fenilo es opcionalmente sustituido con uno o dos grupos seleccionados de halo, alquilo de (C_1-C_6), alcoxi de (C_1-C_6), OH, nitro y ciano,

piperidinilo opcionalmente sustituido en C con halo y opcionalmente sustituido con C o N con alquilo de (C_1-C_6), alcoxi de (C_1-C_6), nitro, o ciano,

tetrahidropiran-4-ilo;

R^{10} es H o metilo;

o

R^9 y R^{10} pueden formar, junto con el carbono al que se unen, un anillo carbocíclico de 3 a 6 miembros,

R^8 es hidrógeno, alquilo de (C_1-C_6), hidroxi o metoxi;

R^5 se selecciona de H, alquilo de (C_1-C_6), e hidroxi-alquilo de (C_1-C_6);

R^{11} se selecciona de H, alquilo de (C_1-C_6), e hidroxi-alquilo de (C_1-C_6);

4.- El compuesto de la fórmula 1, en donde

Q es S;

(A) es un anillo fusionado seleccionado de un anillo aromático de 6 miembros conteniendo 0 ó 1 átomos de N;

R^1 es independientemente seleccionado de halo, alquilo de (C_1-C_6), alcoxi de (C_1-C_6), nitro, ciano, haloalquilo de (C_1-C_6), haloalcoxi de (C_1-C_6), aminocarbonilo, alquilaminocarbonilo de (C_1-C_6), bis{alquilo(C_1-C_6)] aminocarbonilo, aminosulfonilo, alquilaminosulfonilo de (C_1-C_6), bis[alquilo de (C_1-C_6)] aminosulfonilo, alquilcarbonilamino de (C_1-C_6), alquilsulfonilo de (C_1-C_6), alquilsulfonilamino de (C_1-C_6), hidroxi-alquilaminocarbonilo de (C_2-C_6), 1-morfolinilcarbonilo, y 1-piperidinilcarbonilo, y Cuando dos de dichos sustituyentes de R^1 son alquilo de (C_1-C_6), y se unen a átomos de carbono adyacentes del Anillo A, pueden unirse para formar un anillo carbocíclico de 5-7 miembros;

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n es 0, 1, ó 2;

R^2 y R^3 se seleccionan independientemente de hidrógeno, halo, hidroxi, alquilo de (C_1-C_6), trifluorometilo, alcoxi de (C_1-C_6), y trifluorometoxi;

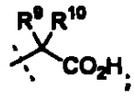
R^4 se selecciona de



en donde:

R^6 es H o CH_3;

y

R^7 es  ;

en donde

R^9 se selecciona de

Alquilo de (C_1-C_6) opcionalmente sustituido con uno o dos grupos seleccionados de vinilo, CF_3, OH, metoxi, SCH_3, NH_2, $-CO_2H$, y $-CONH_2$,

Fenilo de $(CH_2)_m$ en donde m es de 0 a 3, y

En donde el anillo de fenilo es opcionalmente sustituido con uno o dos grupos seleccionados de halo,

alquilo de (C_1-C_6), alcoxi de (C_1-C_6), OH, nitro y ciano,

piperidinilo opcionalmente sustituido en C con halo y opcionalmente sustituido con C o N con alquilo de (C_1-C_6), alcoxi de (C_1-C_6), nitro, o ciano,

tetrahidropiran-4-ilo;

R^{10} es H o metilo;

o

R^9 y R^{10} pueden formar, junto con el carbono al que se unen, un anillo carbocíclico de 3 a 6 miembros,

R^8 es hidrógeno, alquilo de (C_1-C_6), hidroxi o metoxi;

R^5 se selecciona de H, alquilo de (C_1-C_6), e hidroxi-alquilo de (C_1-C_6);

R^{11} se selecciona de H, alquilo de (C_1-C_6), e hidroxi-alquilo de (C_1-C_6);

5.- El compuesto de la reivindicación 1, seleccionado de

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina,

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N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina,

N-({3-cloro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-valina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-valina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-leucina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-leucina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-leucina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)L-leucina,

N-({3-cloro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-leucina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-leucina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-leucina,

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N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-D-leucina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-D-leucina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-isoleucina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-isoleucina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil-isoleucina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-fenilalanina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-fenilalanina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-fenilalanina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-fenilalanina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)L-fenilalanina,

N-({3-cloro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-fenilalanina,

1-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-prolina,

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1-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-prolina,

1-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-prolina,

1-({3-cloro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-prolina,

1-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-prolina,

1-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-prolina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-2-metilalanina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-2-metilalanina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-2-metilalanina,

N-({3-cloro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-2-metilalanina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino)-3-metilbifenil-4-il}carbonil)-2-metilalanina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino)-3-metilbifenil-4-il}carbonil)-2-metilalanina,

Acido 1-[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino)bifenil-4-il}carbonil)amino)ciclopropan-carboxílico,

Acido 1-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]ciclopropancarboxílico,

Acido 1-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)amino]ciclopropan-carboxílico,

Acido 1-[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]ciclopentancarboxílico,

Acido 1-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]ciclopentancarboxílico,

Acido 1-[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]ciclohexan-carboxílico,

Acido(2S)-2-[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]butanoico,

Acido (2S)-2-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]butanoico,

Acido (2S)-2-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)amino]butanoico,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-norvalina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-norvalina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)L-norvalina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-3-metil-L-valina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-3-metil-L-valina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino)-3-metoxibifenil-4-il}carbonil)3-metil-L-valina,

4-cloro-N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino)bifenil-4-il}carbonil)fenilalanina,

Acido (2S)-ciclohexil[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino)bifenil-4-il}carbonil)amino)acético,

Acido [({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino](tetrahidro-2H-piran-4-il)acético,

Acido (1-(tert-butoxicarbonil)piperidin-4-il][({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]acético,

Acido [1-(tert-butoxicarbonil)piperidin-3-il][({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]acético,

Acido [({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino](piperidin-3-il)acético,

Acido 1-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)piperidina-2-carboxílico,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-valina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-valina,

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N-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-valina,

N-{[4'-(1,3-benzotiazol-2-ilamino)-3-metilbifenil-4-il]carbonil}-L-valina,

N-({4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-valina,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-valina,

N-({4'-[(7-fluoro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-valina,

N-({4'-[(7-cloro-1,3-benzotiazol-2-il)amino]-3-metilbifenil-4-il}carbonil)-L-valina,

N-{[4'-(1,3-benzotiazol-2-ilamino)-3-metoxibifenil-4-il]carbonil}-L-valina,

N-{[4'-(1,3-benzotiazol-2-ilamino)bifenil-4-il]carbonil}-L-valina,

N-{[4'-(1,3-benzotiazol-2-ilamino)bifenil-4-il]carbonil}-D-valina,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-valina,

N-({4'-[(7-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-valina,

N-({4'-[(7-cloro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-valina,

316

N-({4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-valina,

N-{[4'-(1,3-benzotiazol-2-ilamino)-3-clorobifenil-4-il]carbonil}-L-valina,

N-({3-cloro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina,

N-({3-cloro-4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina,

N-({3-cloro-4'-[(7-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina,

N-({3-cloro-4'-[(7-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina,

N-{[4'-(1,3-benzotiazol-2-ilamino)-3-metoxibifenil-4-il]carbonil}-L-leucina,

N-({3-metoxi-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-leucina,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-leucina,

N-({4'-[(4-cloro-6-fluoro-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-leucina,

N-({3-metoxi-4'-[(6-nitro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-leucina,

N-[(3-metoxi-4'-{[6-(metilsulfonil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-leucina,

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N-({4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]-3-metoxibifenil-4-il}carbonil)-L-leucina,

N-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-2-metilalanina,

N-{[4'-(1,3-benzotiazol-2-ilamino)bifenil-4-il]carbonil}-2-metilalanina,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-2-metilalanina,

N-{[4'-(1,3-benzotiazol-2-ilamino)bifenil-4-il]carbonil}-N-metil-L-alanina,

N-{[4'-(1,3-benzotiazol-2-ilamino)bifenil-4-il]carbonil}-N-metil-L-valina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alotreonina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alotreonina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-treonina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-treonina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-serina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-O-metil-L-serina,

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3-ciclopropil-N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-O-metil-L-serina,

3-ciclopropil-N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-N-metil-L-valina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-N-metil-L-valina,

N-({3-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina,

N-({3-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-leucina,

N-({3-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-3-metil-L-valina,

N-({3-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-isoleucina,

N-({3-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-norvalina, (

Acido (2S)-2-[({3-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]butanoico,

3-ciclopropil-N-({3-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina,

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N-({3,3'-difluoro-4'-[(6-fluoro-I,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina,

N-({3,3'-difluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-leucina,

N-({3,3'-difluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-3-metil-L-valina,

N-({3,3'-difluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-norvalina,

Acido (2S)-2-[({3,3'-difluoro-4'-[(6-fluoro-I,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]butanoico,

3-ciclopropil-N-({3,3'-difluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina,

N-[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-valina,

N-[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-leucina,

N-[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-norvalina,

N-[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-isoleucina,

N-[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-3-metil-L-valina,

3-ciclopropil-N-[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-alanina,

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Acido (2S)-2-{[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]amino}butanoico,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluoro-bifenil-4-il}carbonil)-L-leucina,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-leucina,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-norvalina,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-isoleucina,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-3-metil-L-valina,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluorobifenil-4-il}carbonil)-L-valina,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluoro bifenil-4-il}carbonil)-L-norvalina,

Acido (2S)-2-[({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluorobifenil-4-il}carbonil)amino]butanoico,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-3-ciclopropil-L-alanina,

N-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluoro bifenil-4-il}carbonil)-3-metil-L-valina,

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Acido (2S)-2-[({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]butanoico,

N-{[4'-([1,3]tiazolo[5,4-b]piridin-2-ilamino)bifenil-4-il]carbonil}-L-valina,N-{[4'-([1,3]tiazolo[4,5-c]piridin-2-ilamino)bifenil-4-il]carbonil}-L-valina,

N-{[4'-([1,3]tiazolo[4,5-b]piridin-2-ilamino)bifenil-4-il]carbonil}-L-valina,

N-[(3'-fluoro-4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil]-L-valina,

N-{[3'-fluoro-4'-([1,3]tiazolo[4,5-c]piridin-2-ilamino)bifenil-4-il]carbonil}-L-valina,

N-{[3'-fluoro-4'-([1,3]tiazolo[4,5-b]piridin-2-ilamino)bifenil-4-il]carbonil}-L-valina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-O-metil-L-alotreonina,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-N-metil-L-norvalina,

Acido 4,4,4-trifluoro-2-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]butanoico,

N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-4-metilen-L-norvalina,

3-ciclobutil-N-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina,

Acido (2S)-[({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino](fenil)acético,

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N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-O-metil-L-alotreonina,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-N-metil-L-norvalina,

Acido 1-[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)(metil)amino]ciclopropan-carboxílico,

Acido (4R)-3-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-5,5-dimetil-1,3-tiazolidina-4-carboxílico,

Acido 4,4,4-trifluoro-2-[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]butanoico,

N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-4-metilen-L-norvalina,

3-ciclobutil-N-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina,

Acido (2S)-[({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino](fenil)acético,

N-[(3'-fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-valina,

N-[(3'-fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-leucina,

N-[(3'-fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-norvalina,

N-[(3'-fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]3-metil-L-valina,

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Acido (2S)-2-{[(3'-fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]amino}butanoico,

N-[(3'-fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-isoleucina,

3-ciclopropil-N-[(3'-fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-alanina,

N-[(4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-valina,

N-[(4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-leucina,

N-[(4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-norvalina,

3-metil-N-[(4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-valina,

Acido (2S)-2-{[(4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]amino}butanoico,

N-[(4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-isoleucina,

3-ciclopropil-N-[(4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}bifenil-4-il)carbonil]-L-alanina,

N-({3'-fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-valina,

N-({3'-fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-leucina,

N-({3'-fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-norvalina,

Acido (2S)-2-[({3'-fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)amino]butanoico,

N-({3'-fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-3-metil-L-valina,

N-({3'-fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-isoleucina,

3-ciclopropil-N-({3'-fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)-L-alanina,

N-[(4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil-L-leucina,

N-[(4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carboni-L-norvalina,

3-metil-N-[(4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil]-L-valina,

Acido (2S)-2-{[(4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil]amino}butanoico,

N-[(4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil-L-isoleucina,

3-ciclopropil-N-[(4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifen)4-il)carbonil]-L-alanina,

N-[(3'-fluoro-4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil]-L-leucina,

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N-[(3'-fluoro-4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil]-L-norvalina,

N-[(3'-fluoro-4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil]-3-metil-L-valina,

Acido (2S)-2-{[(3'-fluoro-4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil]amino}butanoico,

N-[(3'-fluoro-4'-{[6-(trifluorometil)[1,3]tiazolo[4,5-b]piridin-2-il]amino}bifenil-4-il)carbonil]-L-isoleucina, y

N-({4'-[(7-cloro[1,3]tiazolo[5,4-c]piridin-2-il)amino]-3'-fluorobifenil-4-il}carbonil)-L-valina.

6.- Una composición farmacéutica que comprende una cantidad efectiva de un compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en combinación con un vehículo farmacéuticamente aceptable.

7.- Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en combinación con un vehículo farmacéuticamente aceptable y uno o más agentes farmacéuticos.

8.- La composición farmacéutica de la reivindicción 7, en donde dicho agente farmacéutico se selecciona del grupo que consiste de ligandos de PPAR, secretagogos de insulina, fármacos de sulfonilurea, inhibidores de α-glucosidasa, sensibilizadores de insulina, compuestos que disminuyen

salida de glucosa hepática, insulina y derivados de insulina, biguanidas, proteína tirosina fosfatasa - 1B, dipeptidil peptidasa IV, inhibidores de 11beta-HSD, fármacos contra obesidad, inhibidores de HMG-CoA reductasa, ácido nicotínico, fármacos de disminución de lípidos, inhibidores de ACAT, secuestradores de ácidos biliares, inhibidores de reabsorción de ácido biliar, inhibidores de transporte de triglicéridos microsomales, derivados de ácido fíbrico, bloqueadores β, inhibidores de ACE, bloqueadores de canales de calcio, diuréticos, inhibidores de renina, antagonistas de receptor AT-1, antagonistas de receptor de ET, inhibidores de endopeptidasa neutra, inhibidores de vasopepsidasa y nitratos.

9.- La composición farmacéutica de la reivindicción 7, en donde dicho agente farmacéutico se selecciona de agonistas receptores adrenérgicos β-3, antagonistas canabinoides, antagonistas de receptor neuropéptido - Y, inhibidores de neuropéptidos Y5, inhibidores de apo-B/MTP, inhibidores de 11β-hidroxi esteroide deshidrogenasa-1, péptido YY_{3-36} o análogos de los mismos, agonistas de MCR4, agonistas de CCK-A, inhibidores de reabsorción de monoamina, agentes simpatomiméticos, agonistas de dopamina, análogos de receptor de hormona estimulante de melanocitos, antagonistas de hormona de concentración de melanina, leptina, análogos de leptina, agonistas de receptores de leptina, antagonistas de

galanina, inhibidores de lipasa, agonistas de bombesina, agentes tiromiméticos, deshidroepiandroesterona o análogos de la misma, antagonistas del receptor de glucocorticoide, antagonistas de receptor de orexina, factor neurotrófico ciliar, antagonistas de receptor de ghrelina, antagonistas de receptor de histamina-3, agonistas de receptor de neuromedina U, supresores de apetito y compuesto que modula digestión y/o metabolismo.

10.- Un método para regular absorción de alimentos que comprende administrar a un sujeto que necesita del mismo una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 o una composición de la reivindicación 5.

11.- Un método para tratar obesidad o trastornos relacionados con obesidad que comprenden administrar a un sujeto que necesita el mismo una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 o una composición farmacéutica del compuesto de la reivindicación 1 o una composición de la reivindicación 5.

12.- Un método para tratar diabetes o trastornos relacionados con diabetes que comprende administrar a un sujeto que necesita el mismo una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 o una composición farmacéutica de la reivindicación 5.

13.- El método de la reivindicción 12, en donde la diabetes se selecciona del grupo que consiste de diabetes

tipo 1, diabetes tipo 2, diabetes al inicio de madurez de los jóvenes, diabetes autoinmune latente de adultos y diabetes gestacional.

14.- El método de la reivindicación 12, en donde el trastorno relacionado con diabetes se selecciona del grupo que consiste de hiperglicemia, hiperinsulinemia, tolerancia deteriorada a la glucosa, glucosa deteriorada por ayuno, dislipidemia, hipertrigliceridemia y resistencia a insulina.

15.- Un método para regular absorción de alimentos que comprende administrar a un sujeto que necesita el mismo una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 en combinación con uno o más agentes farmacéuticos.

16.- Un método para tratar obesidad y trastornos relacionados con obesidad que comprende administrar a un sujeto que necesita del mismo una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 en combinación con uno o más agentes farmacológicos.

17.- El método de la reivindicación 15 ó 16, en donde el agente farmacéutico se selecciona de agonistas receptores adrenérgicos β-3, antagonistas canabinoides, antagonistas del receptor de neuropeptido-Y, inhibidores de neuropéptido Y5, inhibidores apo-B/MTP, inhibidores de 11β-hidroxi esteroide deshidrogenasa-1, péptido YY_{3-36} o análogos del mismo, agonistas de MCR4, agonistas de CCK-A, inhibidores

de reabsorción de monoamina, agentes simpatomiméticos, agonistas de dopamina, análogos del receptor de hormona estimulante de melanocitos, antagonistas de hormona de concentración de melanina, leptina, análogos de leptina, agonistas del receptor de leptina, antagonistas de galanina, inhibidores de lipasa, agonistas de bombesina, agentes tiromiméticos, deshidroepiandrosterona o análogos de la misma, antagonistas del receptor de glucocorticoides, antagonistas del receptor de orexina, factor neurotrófico ciliar, antagonistas del receptor de ghrelina, antagonistas del receptor de histamina-3, agonistas del receptor de neuromedina U, supresores de apetito, y compuesto que modula digestión y/o metabolismo.

18.- Un método para tratar diabetes o trastornos relacionados con diabetes que comprende administrar a un sujeto que necesita del mismo una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 en combinación con uno mis agentes farmacéuticos.

19.- El método de la reivindicación 18, en donde dicho agente farmacéutico se selecciona del grupo que consiste de agonistas de PPAR, fármacos de sulfonilurea, secretagogos sin sulfonilurea, inhibidores de α-glucosidasa, sensibilizadores de insulina, secretagogos de insulina, compuestos que disminuyen salida de glucosa hepática, insulina y agentes contra obesidad.

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20.- El método de la reivindicación 18, en donde dicha diabetes se selecciona del grupo que consiste de diabetes tipo 1, diabetes tipo 2, diabetes al inicio de madurez de los jóvenes, diabetes autoinmune latente en adultos, y diabetes gestacional.

21.- El método de la reivindicación 18, en donde el trastorno relacionado con diabetes se selecciona del grupo que consiste de hiperglicemia, hiperinsulinemia, tolerancia deteriorada de glucosa, glucosa deteriorada por ayuno, dislipidemia, hipertrigliceridemia y resistencia a insulina.

22.- Un método para tratar obesidad, trastornos relacionados con obesidad, diabetes, o trastornos relacionados con diabetes que comprenden administrar a un sujeto que necesita del mismo una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 en combinación con uno o más agentes seleccionados del grupo que consiste de inhibidores de HMG-CoA reductasa, ácido nicotínico, fármacos que disminuyen lípidos, inhibidores de ACAT, secuestradores de ácido biliar, inhibidores de reabsorción de ácido biliar, inhibidores de transporte de triglicéridos microsomal, derivados de ácido fíbrico, bloqueadores β, inhibidores ACE, bloqueadores de canal de calcio, diuréticos, inhibidores de renina, antagonistas del receptor de AT-1, antagonistas de receptor de ET, inhibidores

de endopeptidasa neutral, inhibidores de vasopepsidasa y nitratos.

23.- El método de la reivindicación 22, en donde dicho trastorno relacionado con diabetes se selecciona del grupo que consiste de hiperglicemia, hiperinsulinemia, tolerancia de glucosa deteriorada, glucosa deteriorada por ayuno, dislipidemia, hipertrigliceridemia, y resistencia a insulina.

24.- El método de cualquiera de las reivindicaciones 15 a 23, en donde el compuesto de la reivindicación 1 y uno o más agentes farmacéuticos se administraron como una sola formulación de dosis farmacéutica.

25.- Un método para tratar enfermedad cardiovascular que comprende administrar a un sujeto que necesita del mismo una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 o una composición farmacéutica de la reivindicación 5.

26.- El método de la reivindicación 25, en donde dicha enfermedad cardiovascular se selecciona de aterosclerosis, enfermedad cardiaca coronaria, enfermedad de arterias coronarias e hipertensión.

27.- Los compuestos de acuerdo con la reivindicación 1, para el tratamiento y/o profilaxis de obesidad, trastornos relacionados con obesidad, diabetes o

trastornos relacionados con diabetes, o enfermedad cardiovascular.

28.- Medicamento que contiene por lo menos un compuesto de acuerdo con la reivindicación 1, en combinación con por lo menos un vehículo o excipiente farmacéuticamente seguro, farmacéuticamente aceptable.

29.- Uso de compuestos de acuerdo con la reivindicación 1 para manufacturar un medicamento para el tratamiento y/o profilaxis de diabetes, trastornos relacionados con diabetes, obesidad, trastornos relacionados con obesidad, o enfermedad cardiovascular.

30.- Medicamentos de acuerdo con la reivindicación 28, para el tratamiento y/o profilaxis de obesidad, trastornos relacionados con obesidad, diabetes, trastornos relacionados con obesidad o enfermedad cardiovascular.

31.- Un método para tratar enfermedades o trastornos asociados con DGAT-1 que comprende administrar a un sujeto que necesita del mismo una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 o una composición de la reivindicación 5.

32.- Un método para tratar enfermedades o trastornos asociados con DGAT-1 que comprende administrar a un sujeto que necesita del mismo una cantidad terapéuticamente efectiva de un compuesto de la

reivindicación 1 en combinación con uno o más agentes farmacéuticos.

RESUMEN

Esta invención se refiere a ciertos compuestos de ácido bifenil-4-il carbonilamino, composiciones y métodos para tratar o prevenir obesidad y enfermedades relacionadas.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/37215

A. CLASSIFICATION OF SUBJECT MATTER
IPC: C07D 277/82(2006.01)

USPC: 548/161
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)
U.S. : 548/161

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 practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	Database CAS ONLINE on STN, Chem. Abstr., Accession No.2004:964835, US2004224997, Preparation of benzazolylaminobiphenyloxoalkanoates; SMITH et al..11 November 2004 (11.11.2004), abstract.	5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent 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
22 March 2006 (22.03.2006)	25 APR 2006
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Rebecca L. Anderson Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/37215

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-4 and 6-31
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:
Please See Continuation Sheet

3. ☒ Claims Nos.: 23
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
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 and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/37215

Continuation of Box II Reason 2:
The numerous variables, e.g. (A, R1, n, Q, R5, R2, R3, R4, R11, R6, R7, R8, R9, R10, etc.) and their voluminous, complex meanings and their virtual incomprehensible permutations and combinations make it impossible to determine the full scope and complete meaning of the claimed subject matter. As presented the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus it is impossible to carry out a meaningful search on same. A search will be carried out on the first discernable invention of claim 5 which is N[((3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl)carbonyl)-L-valine.

Continuation of B. FIELDS SEARCHED Item 3:
CAS ONLINE
STN structure search

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 5221-PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US05/37215	International filing date *(day/month/year)* 14 October 2005 (14.10.2005)	Priority date *(day/month/year)* 15 October 2004 (15.10.2004)
International Patent Classification (IPC) or national classification and IPC IPC: C07D 277/82(2006.01) USPC: 548/161		
Applicant BAYER PHARMACEUTICALS CORPORATION		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of ___ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) ____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18 April 2006 (18.04.2006)	02 August 2006 (02.08.2006)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Rebecca L. Anderson J. Roberts for Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US05/37215

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ 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 (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☒ the description:
pages 1-103 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the claims:
pages 104-122 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☐ the drawings:
pages NONE as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US05/37215

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. 1-4 and 6-31

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-4 and 6-31 are so unclear that no meaningful opinion could be formed *(specify)*:

Please See Continuation Sheet

☐ 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 said claims Nos. ____ .

☐ 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 Preliminary Examining 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 Preliminary Examining 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) and 13*ter*.2.

☐ 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 Preliminary Examining 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

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US05/37215

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 5	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 5	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 5	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claim 5 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the first compound of the claim , N-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine.

Claim 5 meets the criteria set out in PCT Article 33(4), and thus has industrial applicability because the subject matter claimed can be made or used in industry.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US05/37215

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Section III. Non-establishment of report (description/claims/drawings unclear)
The numerous variables, e.g. (A, R1, n, Q, R5, R2, R3, R4, R11, R6, R7, R8, R9, R10, etc.) and their voluminous, complex meanings and their virtual incomprehensible permutations and combinations make it impossible to determine the full scope and complete meaning of the claimed subject matter. As presented the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus it is impossible to carry out a meaningful examination on same. An examination will be carried out on the first discernable invention of claim 5 which is N[({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)-L-valine.

Retiro Folio 343 "Extracto"

344.
343

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
[redacted]
No. 07-046791- -00000-0000
Fecha: 2007-05-10 16:55:18 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 344

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 23,290
FECHA : MARZO 21 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
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	55800345	21/03/2007	24,023,000.00

***** 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._____

COLO 14125 841 015 0

344

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

[redacted]

No. 07-046791- -00000-0000

Fecha: 2007-05-10 16:55:18 Dep: 2020 NUECREACIONES
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 344

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un.Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha Mayo 10/07.

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Bogotá, D.C., Colombia

345

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 346

2020
Bogotá D.C.,

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
BAYER PHARMACEUTICALS CORPORATION

REFERENCIA	Radicación No.	07 46791
	Solicitud internacional	PCT/US2005/037215
	Fecha inicio fase nacional	15/05/2007
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	3332
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC,

13 JUL. 2007

CLARA C. DE JAIMES
Jefe de la división de Nuevas Creaciones (E)

adpa11