Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

EXPEDIENTE No 05-124380

TÍTULO PREPARACION Y USO DE DERIVADOS DE ALQUILARILO PARA EL TRATAMIENTO DE LA OBESIDAD

51 CLASIFICACIÓN INTERNACIONAL A61K 31/4168 ; C07D 235/30
A61K 31/195

71 SOLICITANTE BAYER PHARMACEUTICALS CORPORATION

DOMICILIO West Heaven, Connecticut, Estados Unidos de América

74 APODERADO EMILIO FERRERO
C.C. 438.019 de Usaquén

22 BOGOTÁ, D C ,

(FORMA P 10)

23 12 05 (15)

9097 Imprenta nacional de Colombia- 2004

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA Y COMERCIO
Radicacion : 05124206 Interesado Folios: 476 ión
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Tramite : 011 PCT-WOINT 379 FASE NAC1 493 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 9-Dic-05

1 SOLICITUD DE:

☒ 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 Heaven, Connecticut 06516 Estados Unidos de América Domicilio: West Heaven, 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@camvp.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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5 PCT (86)

Solicitud Internacional No. PCT/US2004/014036 Fecha: 6 de Mayo 2004
Publicación Internacional No. WO2004/100881 A2 Fecha: 25 de Noviembre 2004

6 **Título (54)**
PREPARACIÓN Y USO DE DERIVADOS DE ALQUILARILO PARA EL TRATAMIENTO DE LA OBESIDAD

7 **Clasificación Internacional (51)** A61K 31/4168 ; C07D 235/30

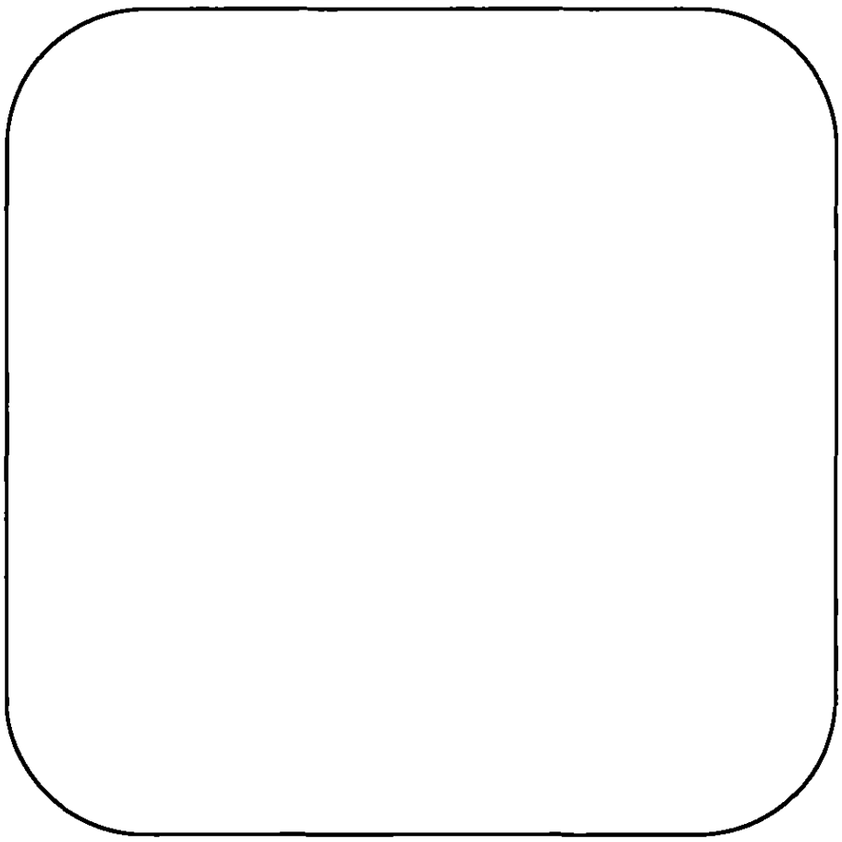
8 **Prioridad** SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	9 de Mayo 2003	60/469,619

9 **Comprobante de pago No.:** 05-87.655 **Fecha:** 15 de Noviembre 2005

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 443.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredite 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

FCC

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2004/087706 A1

   Descripción:

   Páginas 161 en el idioma original

   Páginas 236 en español

   Reivindicaciones: Número (s) 35

   Figuras: Número (s)

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

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a Nº 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-ATTORNEY

14175
5829

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

BAYER PHARMACEUTICALS CORPORATION

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

EL SUSCRITO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE SE TUVO A LA VISTA
31 OCT 2005
NOTARIO SEXTO MEDINA

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4a Nº 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 definitivamente, 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 a los 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 Nº 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 appropriate certificate shall suffice. If any of the appointees were to be definitely absent, 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

6.

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**

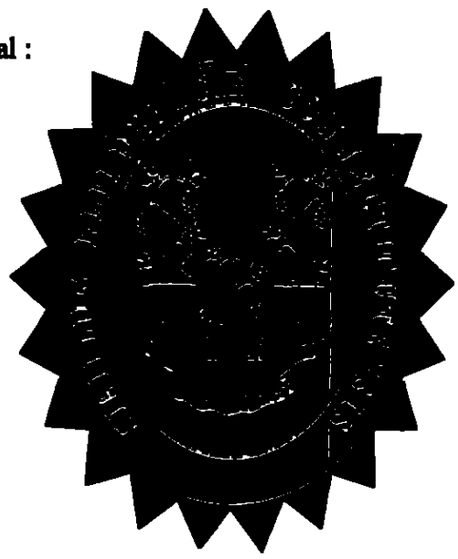
7. by **SUSAN BYSIEWICZ** Secretary of the State of Connecticut

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

31 OCT 2005

8. Number : **2004-1177**

9. Seal :



10. Signature

Susan Bysiewicz

Secretary of the State

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

CONSULADO DE COLOMBIA
31 OCT 2005

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

CERTIFICACIÓN NOTARIAL (SOCIEDAD)

A los 30 días del mes de Enero

de 200 4 compareció(eron) ante mí,

Jeffrey M. Greenman

Secretario Assistente de Bayer Pharmaceutical 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 Gnico 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

31 OCT 2005

MEDINA

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

Elaine Porter
Notary Public
My Commission Expires June 30, 2006

[NOTARIAL SEAL]

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.

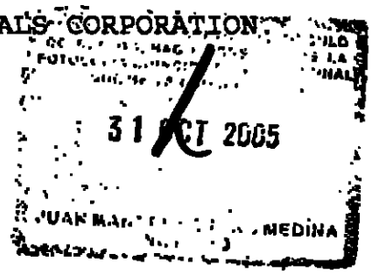
POR: FIRMADO: PAUL R. BERRY, VICE PRESIDENTE, JEFE DE ASUNTOS JURÍDICOS Y SECRETARIO DE BAYER PHARMACEUTICALS CORPORATION.

CERTIFICADO NOTARIAL

ESTADOS UNIDOS DE AMÉRICA

ESTADO DE CONNECTICUT, CONDADO DE NEW HAVEN

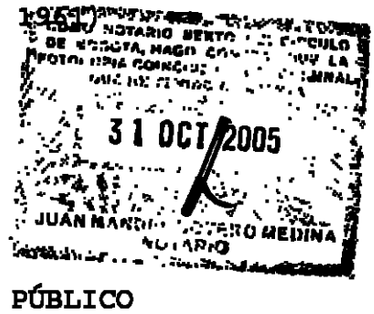
CIUDAD DE WEST HAVEN



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 Calvo M.
Eduardo Calvo Noguera
TRADUCTOR OFICIAL
Res. 341 Febrero de 1994

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE
AGO CONSTAR QUE LA(S) FIRMA(S)

PRESENTADA POR
15 FEB. 2006

PABLO MENDEZ
BARAJAS

MINISTERIO DE RELACIONES
JOSE ASLME
JUEGO DE LUZ
SANTAFE DE BOGOTA D.C.
FEB 16 PM 2
1291
31 OCT 2005

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

(19) World Intellectual Property Organization
International Bureau

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25 November 2004 (25.11.2004)

PCT

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(25) Filing Language: English

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(30) Priority Data:
60/469,619 9 May 2003 (09.05.2003) US

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

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): SMITH, Roger [US/US]; 65 Winterhill Road, Madison, CT 06443 (US). CAMPBELL, Ann-Marie [US/US]; 69 Lynn Drive, Monroe, CT 06468 (US). COISH, Philip [CA/US]; 548 Orange Street, Suite 401, New Haven, CT 06511 (US). DAI, Miao [CN/US]; 83-72 Daniels Street, Briarwood, NY 11435 (US). JENKINS, Susan [US/US]; 50 Bolt Lane, Milford, CT 06460 (US). LOWE, Derek [US/US]; 31 Bittersweet Lane, Hamden, CT 06518 (US). O'CONNOR, Stephen [US/US]; 977 Little Meadow Road, Guilford, CT 06437 (US). SU, Ning [CN/US]; 121 October Hill Road, Hamden, CT 06518 (US). WANG, Gan [CN/US]; 5 Cassella Drive, Wallingford, CT 06492 (US). ZHANG, Mingbao [CN/US]; 75 Nyselius Place, Stamford, CT 06905 (US). ZHU, Lei [US/US]; 101 Oak Ridge Lane, Milford, CT 06460 (US).

(74) Agents: GREENMAN, Jeffrey, M. et al.; Bayer Pharmaceuticals Corporation, 400 Morgan Lane, West Haven, CT 06516 (US).

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

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *without international search report and to be republished upon receipt of that report*

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

(54) Title: PREPARATION AND USE OF ARYL ALKYL ACID DERIVATIVES FOR THE TREATMENT OF OBESITY

(57) Abstract: This invention relates to certain aryl alkyl acid compounds, compositions, and methods for treating or preventing obesity and related diseases.

WO 2004/100881 A2

PREPARATION AND USE OF ARYL ALKYL ACID DERIVATIVES FOR THE TREATMENT OF OBESITY

[001] This application claims benefit of U.S. Provisional Application Serial No. 60/469,619, filed May 9, 2003, the contents of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[002] This invention relates to certain aryl alkyl 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.

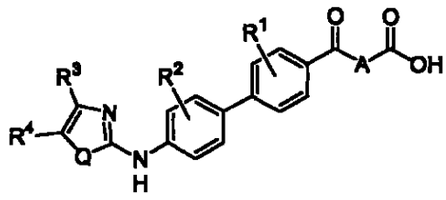
[005] A hallmark characteristic of obesity is an increase in white adipose tissue (WAT) mass that is largely due to accumulation of triacylglycerol. This increase in WAT mass is a key contributor to obesity-associated complications. Diacylglycerol O-acyltransferases (DGATs, EC 2.3.1.2) are membrane-bound 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.

DETAILED DESCRIPTION OF THE INVENTION

[006] The invention relates to aryl alkyl 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.

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

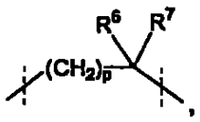


(I)

wherein

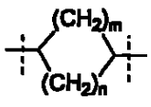
Q is O, S, or NR^5;

A is a linker selected from



wherein p is 1 or 2

and



wherein m is 0 and n is 1, 2, 3, or 4,

or

m is 1 and n is 1, 2, or 3,

and

wherein said linker is optionally substituted by one or two R^8 groups;

R^1 and R^2 are independently selected from hydrogen, halo, (C_1-C_4)alkyl, and (C_1-C_4)alkoxy;

R^3 is selected from

hydrogen,

(C_1-C_6)alkyl optionally substituted by hydroxy,

and

phenyl optionally substituted with (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or halo;

R^4 is selected from hydrogen, nitro, and (C_1-C_6)alkyl;

or

R^3 and R^4 may, when taken together with the carbon atoms to which they are attached, form a benzene ring optionally substituted with up to two substituents 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)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl,

and

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

R^5 is hydrogen or (C_1-C_6)alkyl;

R^6 is hydrogen;

R^7 is hydrogen or (C_1-C_6)alkyl optionally substituted with

(C_1-C_6)alkoxy,

bis[(C_1-C_3)alkyl]amino

or

phenyl optionally substituted with halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

or

R^6 and R^7 are both (C_1-C_6)alkyl;

or

R^6 and R^7 may form, together with the carbon atom to which they are attached,

a 3- to 5-membered carbocyclic ring,

or

a 6-membered ring represented by



wherein W is CH_2, $C(CH_3)_2$, O, NR^9, S, or SO_2;

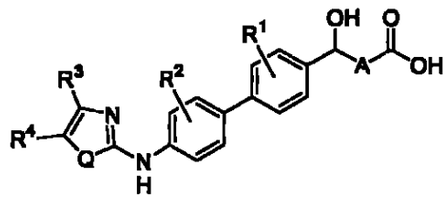
R^8 is $(C_1$-$C_6)$alkyl;

and

R^9 is hydrogen or $(C_1$-$C_6)$alkyl;

or the pharmaceutically acceptable salts and esters thereof.

[008] A second embodiment of this invention is a compound of Formula (Ia)



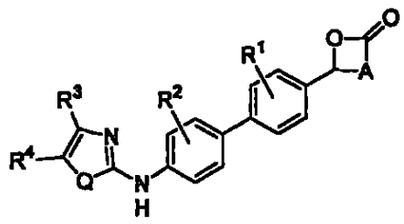
(Ia)

wherein

Q, A, and R^1-R^4 have the meanings as described above for Formula (I)

or the pharmaceutical salts and esters thereof.

[009] A third embodiment of the invention is a compound of Formula (Ib)



(Ib)

wherein

Q, A, and R^1-R^4 have the meanings as described above for Formula (I),

or pharmaceutical salts and esters thereof.

[010] Examples of the invention may be found in the Examples described below and in Tables 1 and 2. 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.

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

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

[013] The terms "(C_1-C_6)alkyl," and "(C_2-C_6)alkyl" mean a linear or branched saturated hydrocarbon groups having from about 1 to about 6 carbon atoms, or from 2 to about 6 carbon atoms, respectively. The hydrocarbon group may also include a cyclic alkyl radical 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.

[014] The term "(C_1-C_6)alkoxy" means a linear or branched saturated hydrocarbon group having from about 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 radical 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.

[015] 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 trifluoromethoxy, difluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 3-fluoropropoxy, 2-chloroethoxy, 3-chloropropoxy, 1-fluoro-2,2,-dichloroethoxy, and the like.

[016] 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 trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, difluoroethyl, 1-fluoro-2,2-dichloroethyl, 3-chloropropyl, 4-bromohexyl, and the like.

[017] 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 carboxamido [$NH_2C(=O)$-], N-methylcarboxamido [$CH_3NHC(=O)$], N-methyl-N-propylcarboxamido [$CH_3CH_2CH_2N(CH_3)C(=O)$-] and N,N-diethylcarboxamido [$(CH_3CH_2)_2NC(=O)$-], and the like.

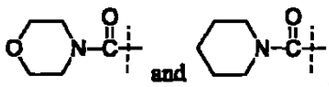
[018] The term "hydroxy-(C_2-C_6)alkylaminocarbonyl" means a carbonyl [C(=O)] group substituted by nitrogen atom in which the nitrogen atom is substituted by a single (C_2-C_6)alkyl group, and said alkyl is further substituted by a hydroxy group. Such groups include 2-hydroxyethylamido-, 3-hydroxypropylamido,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

[019] 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 aminosulfonyl [$NH_2S(=O)_2$-], N-methylaminosulfonyl-[$CH_3NHS(=O)_2$], N-methyl-N-propylaminosulfonyl [$CH_3CH_2CH_2N(CH_3)S(=O)_2$-] and N,N,-diethylaminosulfonyl [$(CH_3CH_2)_2NS(=O)_2$-], and the like.

[020] 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 acetylamino [$CH_3C(=O)NH$-], propanoylamino [$CH_3CH_2C(=O)NH$-],and *t*-butanoylamino [$(CH_3)_2CHC(=O)NH$-]groups, and the like.

[021] 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 methylsulfonylamino [$CH_3S(=O)_2NH$-], propylsulfonylamino [$CH_3CH_2CH_2S(=O)_2NH$-], and *i*-propylsulfonylamino [$(CH_3)_2CHS(=O)_2NH$-] groups, and the like.

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

 and , respectively.

[023] 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.

[024] When any moiety is described as being substituted, it can have one or more of the indicated substituents that can be located at any available position on the moiety. When there are two or more substituents on any moiety, each term shall be defined independently of any other in each occurrence.

[025] Representative salts of the compounds of Formula (I), Formula (Ia), and Formula (Ib) 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.

[026] 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.

[027] The esters in the present invention are non-toxic, pharmaceutically acceptable ester derivatives of the compounds of Formula (I) , Formula (Ia), and Formula (Ib). This includes, for example, ester derivatives of hydroxy-containing compounds of Formula (I) , Formula (Ia), and Formula (Ib) prepared with acetic, benzoic, mandelic, stearic, lactic, salicylic, hydroxynaphthoic, glucoheptonic, and gluconic acid. This also includes, for example, ester derivatives of carboxylic acid-containing compounds of Formula (I) and Formula (Ia) prepared with pharmaceutically acceptable alcohols. Pharmaceutically acceptable alcohols include, but are not limited to methanol, ethanol, isopropanol, butanol, 2-methylpropanol, 2-methoxyethanol, 2-(dimethylamino)ethanol, 2-(diethylamino)ethanol, 2-(1-piperidinyl)ethanol, 2-(1-morpholinyl)ethanol, hydroxyacetic acid, N,N-dimethylglycolamide, hydroxyacetone ,and the like. It will also be apparent to those skilled in the art that compounds of Formula (Ia) are hydroxy acids and therefore may form cyclic esters (i.e., lactones). These esters, including those represented by Formula (Ib), are encompassed within the scope of the invention. The

compounds of Formula (I), Formula (Ia), and Formula (Ib) may be esterified by a variety of conventional procedures well known by those skilled in the art. One skilled in the art would readily know how to successfully carry out these as well as other methods of esterification.

[028] Sensitive or reactive groups on the compounds of Formula (I), Formula (Ia), and Formula (Ib) 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.

[029] 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 which the asymmetric center is in the (*R*)-, (*S*)-, or (*R,S*) configuration.

[030] It will also be appreciated that when two or more asymmetric centers are present in the compounds of the invention, that several diastereomers and enantiomers of the exemplified structures will often be possible, and that pure diastereomers and pure enantiomers represent preferred embodiments. It is intended that pure stereoisomers, pure diastereomers, pure enantiomers, and mixtures thereof, are within the scope of the invention.

[031] 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.

[032] 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.

[033] 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.

[034] 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, for example, in Protective Groups in Organic Synthesis, Second Edition, T. W. Greene, John Wiley and Sons, New York, 1991.

[035] 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."

[036] 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 scheme and Examples below, and by obvious modifications thereto.

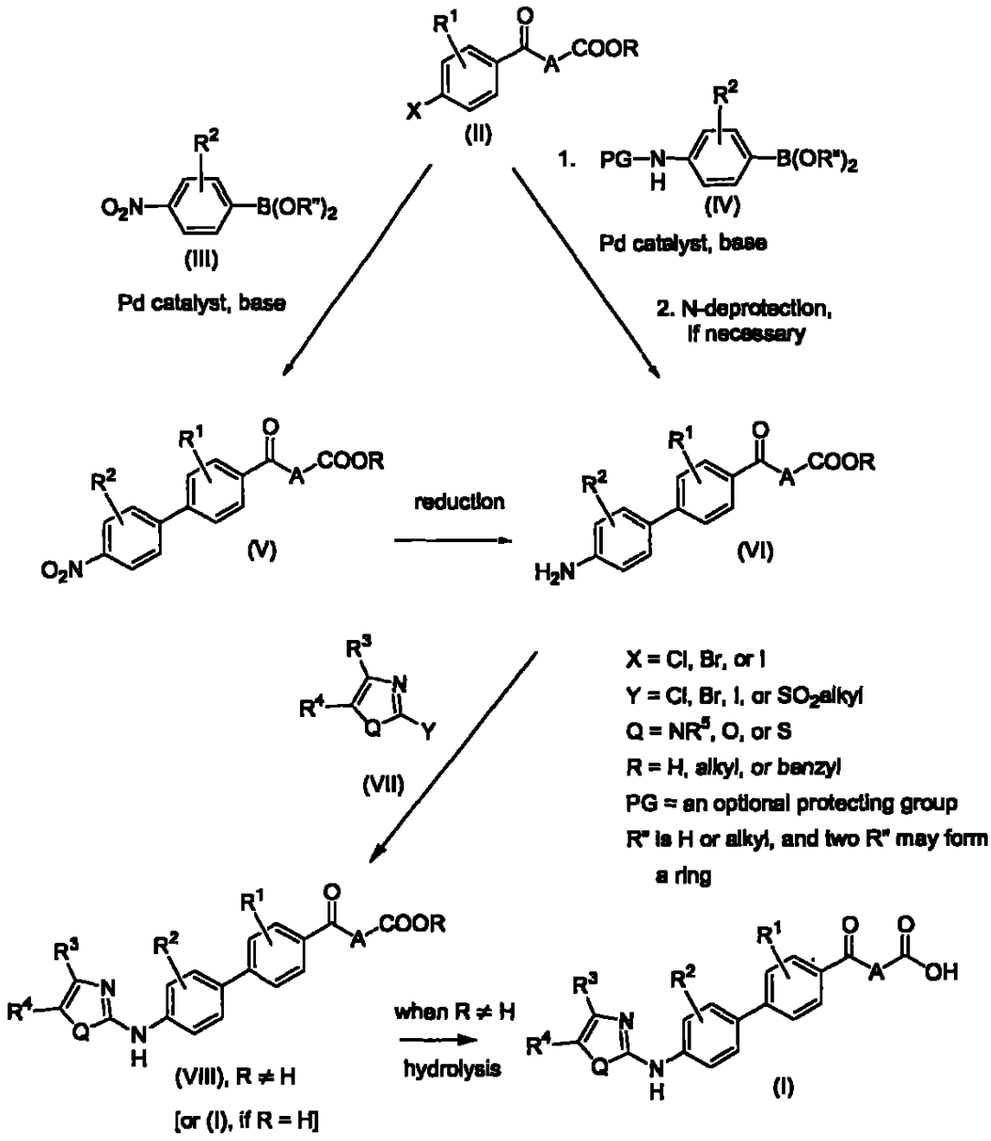
General Preparation of Compounds of the Invention

[037] Preparation of the compounds of the present invention having Formula (I), may be accomplished by either of the two general methods shown below in Reaction Scheme 1 and Reaction Scheme 2.

[038] In Reaction Scheme 1, a coupling reaction of the compound of Formula (II) with nitrophenylboronic acid or boronic ester of Formula (III), in the presence of a palladium catalyst such as $PdCl_2(dppf)$, gives the intermediate of Formula (V). Reduction of the nitro group in the compound of Formula (V) can be accomplished by standard means such as iron/acetic acid to provide the corresponding amino compound of Formula (VI). An alternative route to the compounds of Formula (VI) is to carry out a palladium-catalyzed coupling reaction of the compound of Formula (II) with the optionally protected anilino boronic acid/boronic ester of Formula (IV), followed by deprotection, if necessary, to provide the compound of Formula (VI) directly. The nitro or amino boronic acid/boronic ester reagents (III) and (IV), respectively, are either commercially available or can be prepared from the corresponding readily available halonitrobenzenes by means well known in the art.

[039] The compound of Formula (VI) is then allowed to react with the 2-halo-substituted heterocycle and related compounds of Formula (VII) to give the compounds of Formula (VIII) where $R \neq H$ or Formula (I) when R = H. The Formula (VIII) compounds can be hydrolyzed under standard ester hydrolysis conditions to give the compounds of Formula (I).

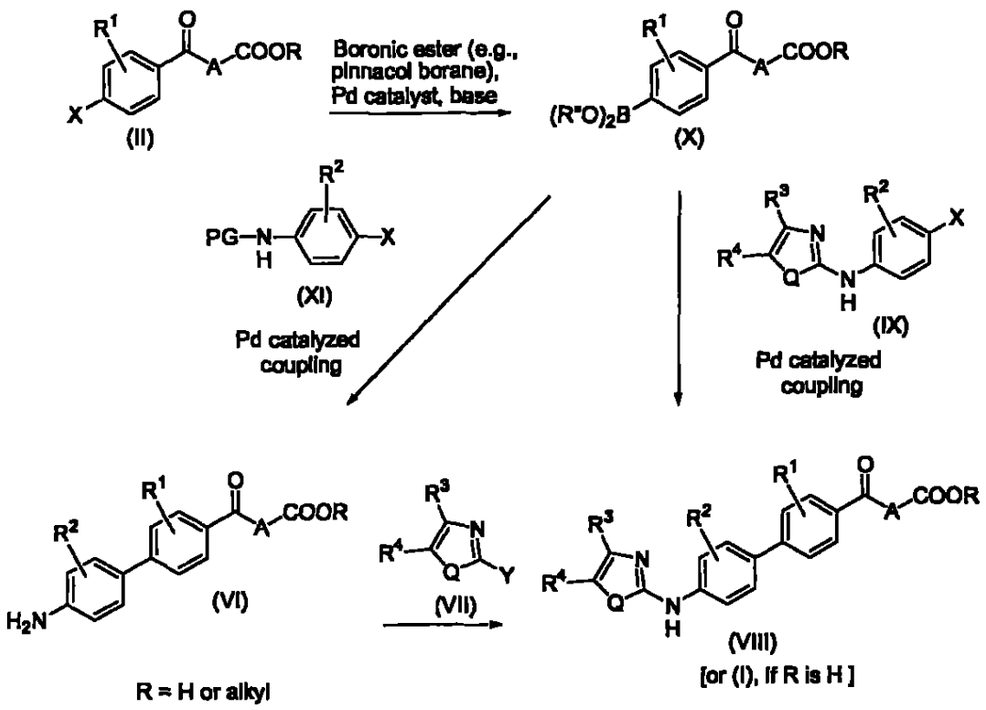
[040] **Reaction Scheme 1**



[041] Alternatives for the preparation of compounds of Formula (VIII), useful when boronic acids or boronic esters of Formulae (III) and (IV) are not readily accessible, are shown in Reaction Scheme 2 below. Preparation of the boronic ester of Formula (X) from the corresponding compound of Formula (II) is accomplished by reaction of (II) with a boronic ester reagent such as pinnacol borane to afford the intermediate of Formula (X). This boronic acid/ester reagent of Formula (X) can be coupled with the 2-anilino-heterocycle of Formula (IX) in the presence of a palladium catalyst and a base such as

potassium carbonate, to give the intermediate of Formula (VIII). The Formula (VIII) compound can also be prepared by carrying out a coupling reaction of (X) with the optionally protected haloaniline of Formula (XI), providing an additional route to the intermediate of Formula (VI). Hydrolysis of (VIII), as described in Reaction Scheme 1, provides the compound of Formula (I).

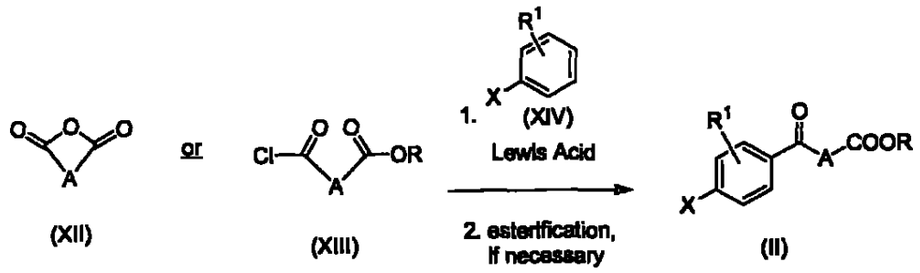
[042] **Reaction Scheme 2**



R = H or alkyl
X = Cl, Br, or I
Y = Cl, Br, I, or SO_2alkyl
Q = NR^5, O, or S
R" = H or alkyl, and two R" may form a ring
PG = an optional protecting group

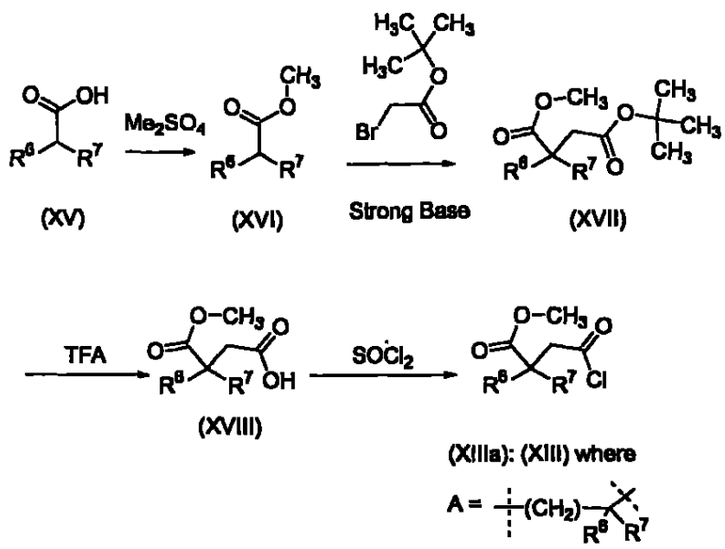
[043] Compounds of Formula (II) may be prepared from a readily available anhydride of Formula (XII) or an acid chloride-ester of Formula (XIII) by a standard Friedel-Crafts acylation reaction as shown in Reaction Scheme 3.

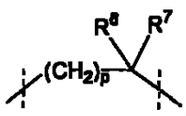
[044] **Reaction Scheme 3**



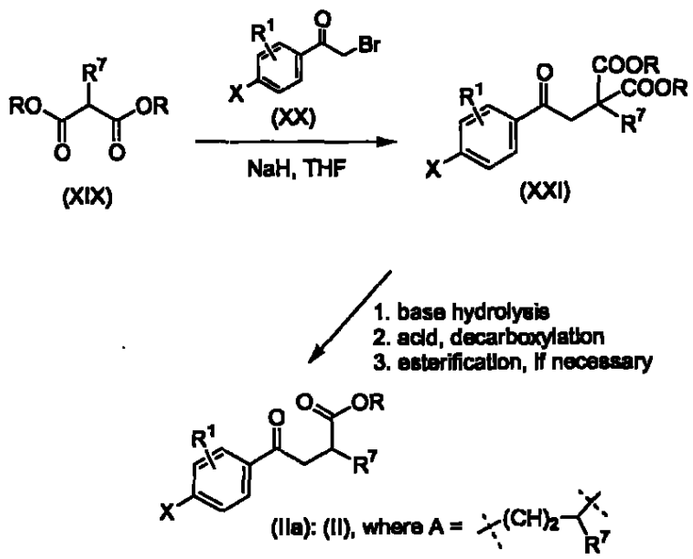
[045] Intermediates of Formula (XIII) are either commercially available or can be prepared in straightforward manner from readily available precursors. A general method of preparation of Formula (XIIIa) [(XIII) where A = -(CH_2)C(R^6)(R^7)-] is shown in Reaction Scheme 4. Esterification of a substituted carboxylic acid of Formula (XV) gives a substituted ester of Formula (XVI); alkylation of the ester with *t*-butyl bromoacetate gives the diester of Formula (XVII). Selective removal of the *t*-butyl group under acidic conditions provides the monoacid monoester of Formula (XVIII) which can be converted by standard means (e.g., $SOCl_2$) to the ester-acid chloride of Formula (XIIIa).

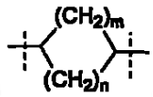
[046] **Reaction Scheme 4**

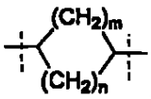


[047] Compounds of Formula (II) in which A is  , R^6 is H, and p is 1, can be prepared as shown in Reaction Scheme 5, by alkylating a substituted malonic ester of Formula (XIX) with the phenacyl bromide of Formula (XX), in the presence of a strong base such as sodium hydride, to give the intermediate of Formula (XXI). Hydrolysis and decarboxylation of (XXI) provides the compound of Formula (IIa) [(II) where A is $-(CH_2)CH(R^7)-$].

[048] **Reaction Scheme 5**



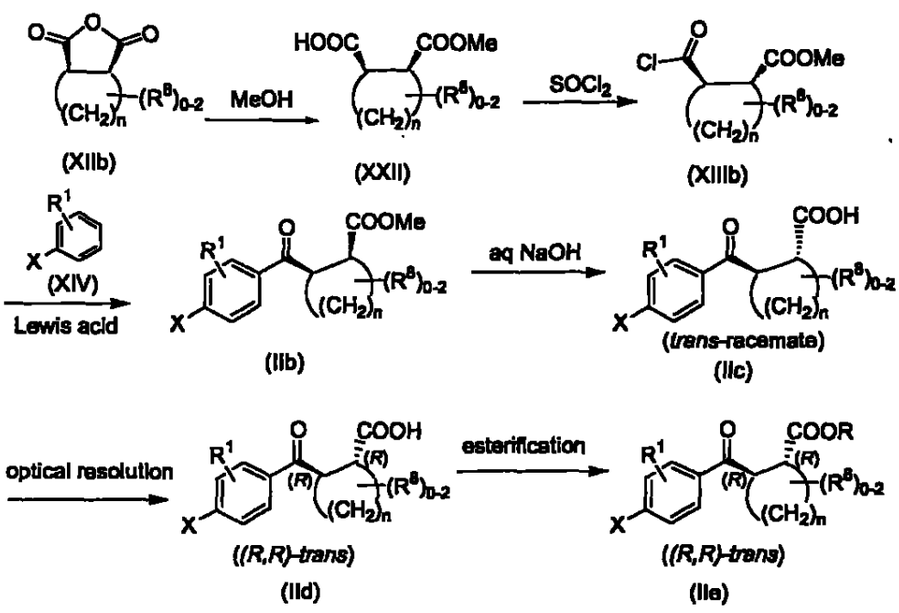
[049] The preparation of Formula (II) compounds in which A is  , m is 0, and n is 1, 2, 3, or 4, and is optionally substituted by up to two R^8 groups is summarized in Reaction Scheme 6. This Reaction Scheme illustrates a general method of obtaining Formula (II) compounds where stereoisomers are possible, and specifically shows the preparation of (*R*,*R*) diastereomers of Formula (IId) and Formula (IIc).

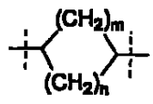
[050] In Reaction Scheme 6, the anhydride of Formula (XIIb) [Formula (XII) where A is  , m is 0, n is 1, 2, 3, or 4, and is optionally substituted by up to two R^8 groups] is converted in two steps to the compound of Formula (XIIIb) [Formula (XIII) where A is defined as above for Formula (XII)]. The method of Reaction Scheme 3 is followed to prepare the compound of Formula (IIb) from (XIIIb). Formula (IIb) may be converted to the compound of Formula (IIc) by basic hydrolysis. If desired, (IIc) may be resolved into its optical antipodes by standard means, for example, via selective crystallization of its diastereomeric salts with an optically active base such as (*R*)- or (*S*)-1-phenylethylamine, and liberating the optically purified compound by acidification of the

salt. Thus, the compound of Formula (IId) can be prepared and converted to the corresponding ester of Formula (Ie).

[051] It is to be understood that intermediates of Formulae (IIb) to (IIe) may be individually carried on to the corresponding Formula (I) compounds by the methods outlined in Reaction Schemes 1 and 2 above, thus allowing the preparation of different diastereomeric compounds of Formula (I).

[052] **Reaction Scheme 6**

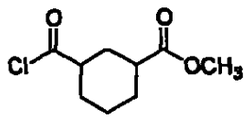


Formula (IIb) - (IIe) represent Formula (II) where A is 

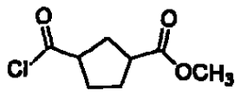
m is 0; n is 1, 2, 3, or 4; and A is optionally substituted by up to two R^8 groups

[053] Other compounds of Formula (II) can be prepared by methods known in the art and by the methods described herein, for example, by using compounds 1 (prepared as described in McDonald, et al., J. Org. Chem. 35:2666-2669, 1970), 2 (prepared as described in Hronowski, et al., Can. J. Chem.66:61-70, 1988), 3 (prepared as described in Chung, et al., Bioorg. Med. Chem. Lett. 5:1097-1102, 1995; Scetz, et al., Rec. Trav. Chim. Pays-Bas 107:160-162, 1988), 4 (prepared as described in Jun, et al., Bull. Korean Chem. Soc. 9:206-209, 1988); 5 (*see, e.g.*, methods described in U.S. Patent

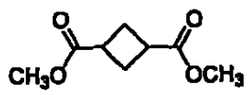
No. 6,562,828); 6 and 7 (*see, e.g.*, methods described in Carlon, et al., Org. Prep. Proc. Int. 9:94-96, 1977; U.S. Patent No. 3,256,277; Bushweller, et al.,. J. Org. Chem. 54:2404-2409, 1989).



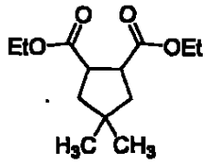
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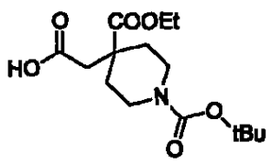
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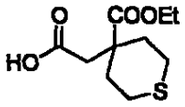
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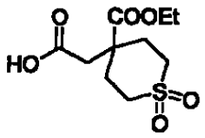
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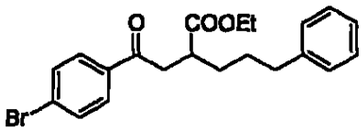


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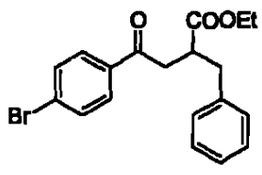


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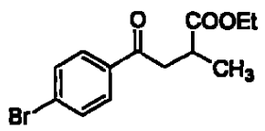
[054] In addition, compounds of Formula (*II*) can be prepared by applying other methods known in the art. For example, to prepare the following specific compounds of Formula (II), designated 8-13, the following methods may be employed: 8 (*see, e.g.*, WO 9615096 and U.S. Patent No. 5,789,434); 9 (*see, e.g.*, methods described in WO 9717317); 10 (*see, e.g.*, methods described in van der Mey, et al., J. Med. Chem. 44:2511-2522, 2001; Gaare, et al., Acta Chem. Scand. 51:1229-1233, 1997; Kuchar, et al., Coll. Czech. Chem. Commun. 51:2617-25, 1986); 11 (*see, e.g.*, methods described in Kawamatsu, et al., Arzneim. Forsch. 30:454-459, 1980; Bajaj, et al., J. Indian Chem. Soc. 52:1076-1078, 1975); 12 and 13 (*see, e.g.*, methods described in WO 9615096, and Sen, et al,. Indian J. Chem. 23B:821-824, 1984).



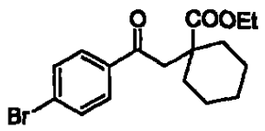
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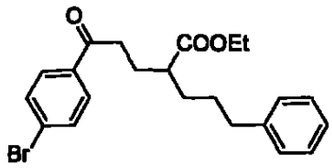
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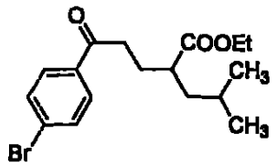
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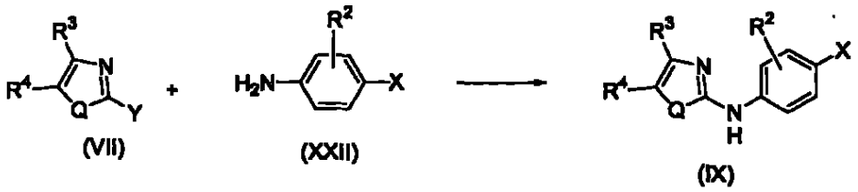
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13

[055] Compounds of Formula (IX) can be prepared by reaction of an aniline of Formula (XXII) by allowing reaction with a compound of Formula (VII), generally by heating together in an inert solvent. This method is illustrated in Reaction Scheme 7.

[056] **Reaction Scheme 7**



(VII) (XXII) (IX)

Y = Br, Cl, I, or SO_2alkyl
X = Cl, Br, or I

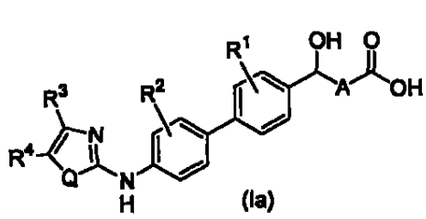
[057] Other compounds of Formula (IX) can be prepared by other methods known in the art, for example, by the reaction of a 2-oxoethyl thiocyanate with an aniline of Formula (XXII) to form a 2-(arylamino)-thiazole as described in the art (Sharma, et al., Tetrahedron, 15:53-59, 1961; Schanti, et al., Synth.Commun. 28:1451-1462, 1998).

[058] Compounds of Formula (VII) can be prepared by methods known in the art, such as the following: (a) 2-chloro-5-cyanobenzothiazole and 2-chloro-6-cyanobenzothiazole (WO 2002000633); (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-benzothiazolecarboxamide, 2-chloro-N-methyl-6-benzothiazolecarboxamide, 2-chloro-N-ethyl-5-benzothiazolecarboxamide, 2-chloro-N,N-dimethyl-5-benzothiazolecarboxamide, 2-chloro-N,N-dimethyl-6-benzothiazolecarboxamide, 2-chloro-N-(2-hydroxyethyl)-5-benzothiazolecarboxamide, 2-

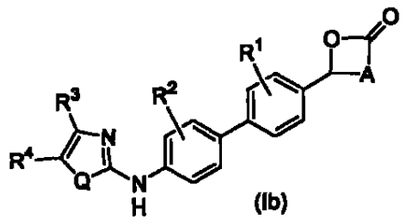
chloro-N-(2-hydroxyethyl)-6-benzothiazolecarboxamide, and 2-chloro-7-morpholinocarbonyl-benzothiazole (U.S. Patent No. 3,654,296); (e) 6-butoxy-2-chloro-benzothiazole (Bordi, et al., Farmaco 49:153-166, 1994); (f) 2-chloro-6-isopropoxy-benzothiazole, 2-chloro-5-cyano-benzoxazole, and 5-cyano-2-methylthiobenzothiazole (Eur. Patent Appl. EP1308439A1); (g) 2-chloro-5-methylsulfonyl-benzoxazole (Lok, et al., J. Org. Chem. 61:3289-3297, 1996); (h) 2-chloro-5-(4-methyl-phenyl)-thiazole, 2-chloro-5-(4-isopropyl-phenyl)-thiazole, and 2-chloro-5-(2,4-dimethyl-phenyl)-thiazole (Morijauian, et al., J. Org. Chem. 51:543-545, 1986; (i) 2-chloro-5-(4-methoxy-phenyl)-thiazole (Fr. Demande FR 2152345); (j) 2-chloro-4,5-dimethylthiazole (Begtrup, et al., Acta Chem. Scand. 46:372-383, 1992); (k) 2-chloro-4-hydroxymethylthiazole (WO 2000078746); (l) 2-chloro-4-methylthiazole (Eur. Pat. Appl. EP1216997); (m) 2-chloro-5-cyanobenzoxazole, 2-chloro-benzimidazole-5-carbonitrile, 2-chloro-5-trifluoromethylbenzimidazole, 2-chloro-5-fluorobenzimidazole, 2,5-dichlorobenzimidazole, 2-chloro-5-nitrobenzimidazole, 2-chloro-1-methylbenzimidazole, 2-chloro-5-trifluoromethyl-1-methylbenzimidazole, and 2-chloro-5-fluoro-1-methylbenzimidazole (Eur. Pat. Appl. EP1308439A1); (n) 2-chloro-1-methyl-benzimidazole, 2-chloro-1-ethyl-benzimidazole, 2-chloro-1-isopropyl-benzimidazole, 2-chloro-1-benzyl-benzimidazole, and 2-chloro-6-fluoro-1-methyl-1-benzimidazole (WO 2001047898); (o) 2-chloro-1-cyclopropyl-benzimidazole (Orjales, et al., J. Med. Chem. 40:586-593, 1997); (p) 2-chloro-7-methoxy-1-isopropyl-benzimidazole and 2-chloro-5-fluoro-1-isopropyl-benzimidazole (Fr. Demande FR 2773800).

[059] The compounds having Formula (Ia) can be prepared from compounds of Formula (I) or Formula (VI), by the use of selective reducing agents and methods for selective reduction known to those skilled in the art. For example, a compound of Formula (I) can be treated with sodium borohydride or similar reducing agent to afford the corresponding compound of Formula (Ia).

[060] Formula (Ib) compounds are prepared from Formula (Ia) compounds by standard methods for lactonization of hydroxy acids (e.g. in the presence of an acid catalyst such as TsOH) in an anhydrous solvent such as toluene.



(Ia)



(Ib)

[061] Examples of the invention may be found in the Examples described below and in Tables 1 and 2. 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.

PREPARATION OF COMPOUNDS OF THE INVENTION

General Information

Mass spectra

[062] 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.

[063] Liquid chromatography – electrospray mass spectra (LC-MS) data were obtained by using one of the following two methods. In the Examples and Tables provided below, the LC-MS data are given with HPLC retention times (ret. time). Except as noted otherwise, Method 1 was used.

[064] Method 1: 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.

[065] Method 2: Gilson HPLC system equipped with two Gilson 306 pumps, a Gilson 215 Autosampler, a Gilson diode array detector, a YMC Pro C-18 column (2 x 23mm, 120 A), and a Micromass LCZ single quadrupole mass spectrometer with z-spray electrospray ionization. Spectra were scanned from 120-800 amu over 1.5 seconds. ELSD (Evaporative Light Scattering Detector) data was also acquired as an analog channel. 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 90% B over 3.5 minutes at a flow rate of 1.5 mL/min was used with an initial hold of 0.5 minutes and a final hold of 0.5 minutes at 90% B. Total run time was 4.8 minutes. An extra switching valve was used for column switching and regeneration.

NMR Spectra

[066] 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 13C spectra.

Chiral Chromatography

[067] Chiral chromatography was carried out by using Pirkle Covalent (R,R) Whelk-O 2 10/100 from Regis Technologies as the stationary phase. The mobile phase consisted of A = Hexane (containing 0.1% TFA) and B = isopropyl alcohol (containing 0.1% TFA). The usual gradient was 10% B to 60% B over 25 minutes. In some cases, a gradient of 10 to 90% B or 50 to 90% B was used. Quantification and fraction collection was based on UV detection at 330 nm (also at 280 nm). Samples were typically dissolved in DMF prior to injection; for analytical work, these sample solutions were diluted further with methanol. For analytical work, a 4.6 x 250 mm column, flow rate = 1 mL/min, and Shimadzu analytical HPLC were used. For preparative work, a 20 x 250 mm column, flow rate = 25 mL/min, and Gilson HPLC were used, with a typical injected sample quantity of 50 mg.

Abbreviations and Acronyms

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

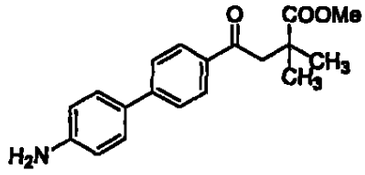
aq	aqueous
BuOH	butanol
$CDCl_3$	deuterated chloroform
Celite®	diatomaceous earth filter agent, ®Celite Corp.
DCE	dichloroethane
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMSO-d_6	deuterated dimethyl sulfoxide-
ee	enantiomeric excess
EI-MS	electron impact – mass spectrometry
ESI-MS	electrospray ionization – mass spectrometry
EtOH	ethanol
EtOAc	ethyl acetate
h	hour(s)
*i*PrOH	isopropanol

GC-MS	gas chromatography – mass spectrometry
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
LC-MS	liquid chromatography – mass spectrometry
MeI	methyl iodide
MeOH	methanol
min	minutes
MS	mass spectroscopy
NMR	nuclear magnetic resonance
$PdCl_2(dppf)$	1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
p.o.	orally administered
Rf	TLC retention factor
rt	room temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

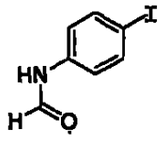
Preparation of Compounds of Formula (II), (V) and (VI)

[069] **Intermediate A**

Methyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate



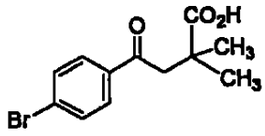
[070] 4-Iodoformanilide



[071] Step 1. To a solution of 4-iodoaniline (30.0 g, 137 mmol) in 100 mL THF and 100 mL toluene, a solution of acetic anhydride (16.0 g, 157 mmol) and formic acid (10.8 g, 235 mmol) was slowly added from an addition funnel under argon atmosphere. The reaction mixture temperature

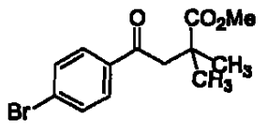
was maintained below 15°C during the addition. After the addition was finished, the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with water (300 mL) and ethyl acetate (200 mL). The organic layer was separated, washed with water (2 x 200 mL), and 200 mL saturated aqueous sodium bicarbonate solution. After drying over sodium sulfate, the mixture was concentrated under reduced pressure to afford 4-iodoformanilide as an off-white solid (33.5 g, >98%). ^{1}H NMR (DMSO-d_6) δ 10.27 (s, 1H), 8.26 (d, J = 2 Hz, 1H), 7.64 (d, J = 12 Hz, 2H), 7.40 (d, J = 11.7 Hz, 2H) and 30% tautomer; ESI-MS m/z 248.0 (MH^+).

[072] 4-(4-Bromophenyl)-2,2-dimethyl-4-oxobutanoic acid



[073] Step 2. To a chilled solution (ice/water bath) of bromobenzene (7.71 g, 49.1 mmol) and 3,3-dimethyldihydro-2,5-furandione (5.99 g, 46.7 mmol) in dichloroethane (150 mL) was added aluminum trichloride (13.28 g, 99.58 mmol). The ice bath was removed and the reaction mixture was stirred at rt overnight. The mixture was again chilled in an ice/water bath, and then quenched with 1 M aqueous hydrochloric acid. Water (70 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage apparatus, 17:83 ethyl acetate/hexane) to give 4-(4-bromophenyl)-2,2-dimethyl-4-oxobutanoic acid as a white solid (8.34 g, 63%). LC-MS: ret. time 2.79 min; m/z 284.8 (MH^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 6H), 3.27 (s, 2H), 7.60 (d, 2H), 7.81 (d, 2H).

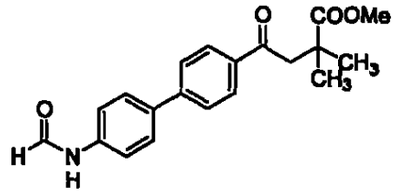
[074] Methyl 4-(4-bromophenyl)-2,2-dimethyl-4-oxobutanoate



[075] Step 3. To a solution of 4-(4-bromophenyl)-2,2-dimethyl-4-oxobutanoic acid (8.33 g, 29.2 mmol) and 2,2-dimethoxypropane (3.95 g, 37.9 mmol) in methanol (100 mL) was added 1 M HCl in dioxane (2.0 mL). The reaction mixture was stirred at 50°C for 22 h. The mixture was concentrated under reduced pressure. Toluene (2 x 60 mL) was added and the mixture concentrated again (2x) to afford methyl 4-(4-bromophenyl)-2,2-dimethyl-4-oxobutanoate as an off-white, semi-solid (8.60 g, 99%). This material was used in the next step without further purification. LC-MS: ret. time 3.23

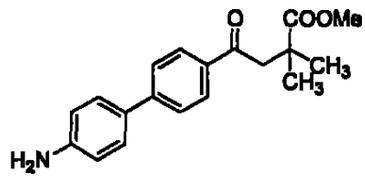
min; *m/z* 298.8 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 6H), 3.28 (s, 2H), 3.67 (s, 3H), 7.58 (d, 2H), 7.78 (d, 2H).

[076] Methyl 4-[4'-(formylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoate



[077] Step 4. To a 2-L three-necked round-bottomed flask, were charged 4-iodoformanilide (30.0 g, 121 mmol, 1.0 eq), bis(pinacolato)diboron (30.8 g, 121 mmol, 1.0 eq), palladium acetate (0.82 g, 3.6 mmol, 3 mol%), potassium acetate (35.70 g, 364.3 mmol), and 500 mL *N,N*-dimethylformamide. The mixture was degassed by gently bubbling argon through the solution for 30 minutes at rt. The mixture was then heated at 80°C under argon until the reaction was complete (2-3 hours). After the mixture was cooled to rt, methyl 4-(4-bromophenyl)-2,2-dimethyl-4-oxobutanoate (36.3 g, 121 mmol), cesium carbonate (59.4 g, 182 mmol), and palladium tetrakistriphenylphosphine (4.2 g, 3.6 mmol, 3 mol%) were added. The reaction mixture was then heated at 80°C overnight under argon. The mixture was cooled to rt, and slowly diluted with water (1.5 L), which caused solid material to precipitate. The solids were removed by filtration, and washed with 500 mL water. Then the solids were dissolved in 500 mL methylene chloride, and black particles were removed by passing the solution through a pad of Celite®. The filtrate was washed with 150 mL water (2x). After the solution was dried over sodium sulfate, the solution was concentrated under reduced pressure to afford a dark, brown residue. The residue was stirred in ethyl acetate (200 mL) and hexane (200 mL) for 1 h. After filtration and drying, methyl 4-[4'-(formylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoate was obtained as a yellow solid (28.0 g, 68%). ^1H NMR ($CDCl_3$) δ 8.42 (d, J = 2 Hz, 1H), 7.98 (d, J = 8 Hz, 2H), 7.62 (m, 6H), 3.70 (s, 3H), 3.33 (s, 2H), 1.35 (s, 6H) and 40% tautomer; ESI-MS *m/z* 340.1 (MH^+).

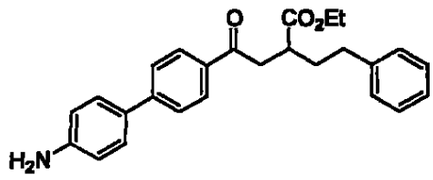
[078] Methyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate



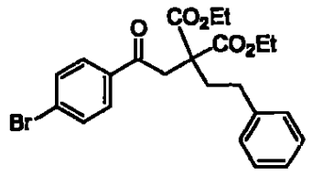
[079] Step 5. To a suspension of methyl 4-[4'-(formylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoate (2.40 g, 7.07 mmol) in 20 mL methanol, was added 7 mL concentrated hydrochloric acid at below rt. The reaction mixture was stirred at rt overnight. The mixture was concentrated under reduced pressure and saturated aqueous sodium bicarbonate solution was slowly added until pH > 8.0. The aqueous layer was then extracted with methylene chloride (2 x 25 mL), and the combined organic layer was dried over sodium sulfate. The mixture was concentrated under reduced pressure to afford methyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate as a light red solid (2.1 g, 95%). ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 9 Hz, 2H), 7.60 (d, J = 9 Hz, 2H), 7.46 (d, J = 9 Hz, 2H), 6.76 (d, J = 9 Hz, 2H), 3.85 (br s, 2H), 3.69 (s, 3H), 3.32 (s, 2H), 1.35 (s, 6H); ESI-MS *m/z* 312.4 (MH^+); HRMS *m/z* calcd for MH^+ 312.1594, found 312.1597.

[080] **Intermediate B**

Ethyl 4-(4'-amino-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenyl-ethyl)butanoate



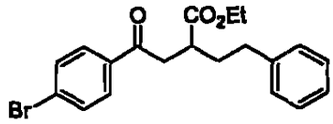
[081] Diethyl 2-[2-(4-bromophenyl)-2-oxoethyl]-2-(2-phenylethyl)-malonate



[082] Step 1. To a 500 mL 3-neck round-bottom flask equipped with an argon inlet and an addition funnel, was added sodium hydride (95%, 1.40 g, 58.3 mmol) followed by tetrahydrofuran (30 mL). The resulting suspension was then cooled to 0°C and diethyl 2-(2-phenylethyl)malonate (14.0 g, 53.0 mmol) in tetrahydrofuran (20 mL) was added dropwise over 20 minutes. The cooling bath was removed and the reaction mixture was allowed to warm to rt over 45 minutes. A solution of 2-bromo-1-(4-bromophenyl)ethanone (14.72 g, 58.26 mmol) in tetrahydrofuran (40 mL) was rapidly added and the resulting orange-red mixture was stirred at rt for 16 h. The mixture was carefully poured into 300 mL of 1N hydrochloric acid, and the resulting mixture was stirred for 10 minutes and extracted twice with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (Biotage flash 75, 10:90 ethyl acetate/hexane) to afford diethyl 2-[2-(4-bromophenyl)-2-oxoethyl]-2-(2-phenylethyl)malonate (14.8 g, 61%). LC-MS ret. time 3.89 min,

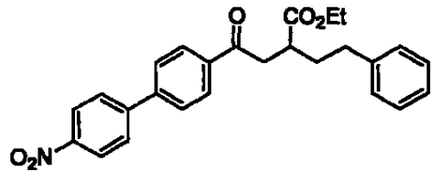
m/z 461.2 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 6H), 2.41-2.45 (m, 2H), 2.56-2.59 (m, 2H), 3.67 (s, 2H), 4.23 (q, 4H), 7.14-7.22 (m, 3H), 7.22 (d, 2H), 7.61 (d, 2H), 7.79 (d, 2H).

[083] Ethyl 4-(4-bromophenyl)-4-oxo-2-(2-phenylethyl)butanoate



[084] Step 2. To a solution of diethyl 2-[2-(4-bromophenyl)-2-oxoethyl]-2-(2-phenylethyl)malonate (7.89 g, 17.1 mmol) in acetone (18.5 mL) and ethanol (17.0 mL) was added 1 N aqueous sodium hydroxide solution (17.1 mL), and the resulting solution was heated at 50°C for 3 h. Solvent was then removed under reduced pressure via rotary evaporation and the resulting residue was further concentrated under high vacuum for 1 h. The residue was redissolved in dimethoxyethane (18.5 mL) and the solution was heated at 80°C for 2.5 h. The mixture was cooled to rt, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under high vacuum. The resulting residue was purified by flash chromatography (Biotage flash 75, 10:90 ethyl acetate/hexane) to afford ethyl 4-(4-bromophenyl)-4-oxo-2-(2-phenylethyl)butanoate (4.32 g, 65%). LC-MS ret. time 3.79 min, *m/z* 389.2 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 3H), 1.78-1.94 (m, 2H), 2.62 (t, 2H), 2.86-3.01 (m, 2H), 3.26-3.36 (m, 1H), 4.10 (q, 2H), 7.05-7.11 (m, 3H), 7.18-7.23 (m, 2H), 7.51 (d, 2H), 7.72 (d, 2H).

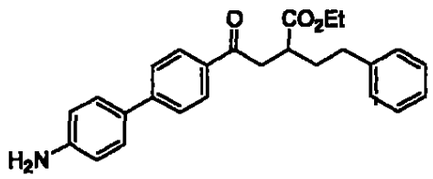
[085] Ethyl 4-(4'-nitro-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenylethyl)butanoate



[086] Step 3. Ethyl 4-(4-bromophenyl)-4-oxo-2-(2-phenylethyl)butanoate (4.32 g, 11.1 mmol) and 4-nitrophenylboronic acid (2.22, 13.3 mmol) was added to a dry flask under argon. Toluene (100 mL), dioxane (25 mL), saturated aqueous sodium carbonate (30 mL), and [1,1'-bis(diphenylphosphino)-ferrocene]dichloro palladium(II) (1:1 complex with dichloromethane, 453 mg, 0.55 mmol) were added and the mixture was thoroughly degassed. The resulting mixture was then heated at 85°C for 16 h before it was cooled to rt. Water was added and the mixture was extracted twice with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage flash 75, 5:1 ethyl acetate / hexane) to afford ethyl 4-(4'-nitro-1,1'-biphenyl-4-yl)-4-oxo-2-(2-

phenylethyl)butanoate (3.6 g, 75%). HPLC ret. time 3.99 min, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H), 1.85-2.08 (m, 2H), 2.71 (t, 2H), 3.05-3.20 (m, 2H), 3.45-3.52 (m, 1H), 4.20 (q, 2H), 7.18-7.31 (m, 5H), 7.72 (d, 2H), 7.78 (d, 2H), 8.05 (d, 2H), 8.33 (d, 2H).

[087] Ethyl 4-(4'-amino-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenyl-ethyl)butanoate

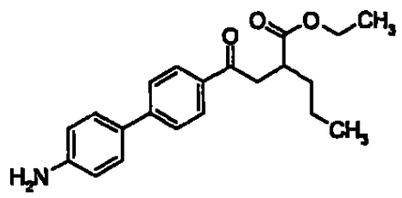


[088] Step 4. To a solution of ethyl 4-(4'-nitro-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenylethyl)butanoate (5.35 g, 12.4 mmol) in 85% ethanol (160 mL) was added iron powder (6.94 g) followed by a 2 N aqueous solution of hydrochloric acid (6.2 mL). The resulting mixture was refluxed for 2.5 h, filtered through a pad of Celite®, and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford ethyl 4-(4'-amino-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenylethyl)butanoate (4.74 g, 95%). LC-MS ret. time 3.22 min, *m/z* 402.0 (MH^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 3H), 1.83-2.10 (m, 2H), 2.65 (t, 2H), 3.03-3.12 (m, 2H), 3.41-3.48 (m, 1H), 4.12 (q, 2H), 6.70 (d, 2H), 7.19 (d, 4H), 7.25 (m, 1H), 7.38 (d, 2H), 7.53 (d, 2H), 7.89 (d, 2H).

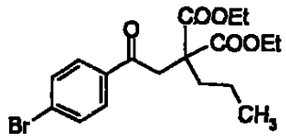
[089] This intermediate compound ethyl 4-(4'-amino-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenylethyl)-butanoate, a racemic mixture, was separated into its two (*R*) and (*S*) enantiomeric isomers by preparative chiral HPLC using a Pirkle Covalent (R,R) Whelk-O 2 10/100 column (25 cm x 21.1 mm), and a solvent elution gradient of 50% isopropanol in hexane to 85% isopropanol in hexane, containing 0.1% trifluoroacetic acid, at a flow rate of 30 mL/min. Monitoring by ultraviolet detection (254 nm) enabled the identification and isolation of enantio-enriched samples of the two isomers, which could be used to prepare individual (*R*) and (*S*) enantiomers of compounds of the invention.

[090] **Intermediate C**

Ethyl 2-[2-(4'-amino-1,1'-biphenyl-4-yl)-2-oxoethyl]pentanoate

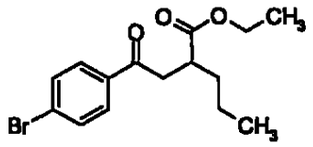


[091] Diethyl 2-[2-(4-bromophenyl)-2-oxoethyl]-2-propylmalonate



[092] Step 1. To a 100 mL 3-neck flask was added sodium hydride (95%, 0.55 g, 22 mmol) followed by tetrahydrofuran (13 mL). The suspension was cooled to 0°C, and a solution of diethyl propylmalonate (4.00 g, 19.8 mmol) in tetrahydrofuran (10 mL) was added dropwise over 10 minutes. The cooling bath was removed and the reaction mixture was allowed to warm to rt over 45 minutes. A solution of 2,4'-bromoacetophenone (5.50 g, 19.8 mmol) in tetrahydrofuran (30 mL) was added via addition funnel over 10 minutes, and the resulting orange-red reaction mixture stirred at rt for 16 h. The reaction mixture was slowly poured into 1.0 N aqueous hydrochloric acid solution (100 mL) cooled to 0°C, stirred for 15 minutes, followed by addition of ethyl acetate (100 mL) and water (100 mL), and the layers separated. The aqueous layer was extracted with additional ethyl acetate (75 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution (75 mL), dried over anhydrous sodium sulfate, filtered *in vacuo* through 2.5 cm Celite®/2.5 cm silica, and the filtrate was concentrated under reduced pressure, to afford diethyl 2-[2-(4-bromophenyl)-2-oxoethyl]-2-propylmalonate (7.62 g, 86%). LC-MS ret. time 3.74 min, *m/z* 399.0 (MH^+); ^1HNMR (300 MHz, $CDCl_3$) δ 0.82-0.98 (m, 3H), 1.10-1.45 (m, 8 H), 2.01-2.12 (m, 2H), 3.60 (s, 2H), 4.10-4.30 (m, 4H), 7.60 (d, 2H), 7.85 (d, 2H).

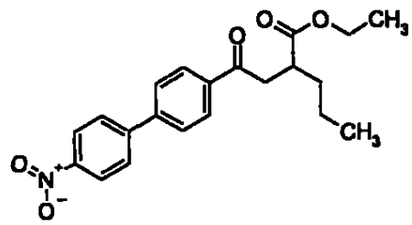
[093] Ethyl 2-[2-(4-bromophenyl)-2-oxoethyl]pentanoate



[094] Step 2. To a 200 mL flask was added crude 2-[2-(4-bromophenyl)-2-oxoethyl]-2-propylmalonate (7.62 g, 19.2 mmol), acetone (21 mL), and ethanol (19 mL), followed by addition of 1 N aqueous sodium hydroxide solution (19.1 mL). The reaction mixture was heated to 55°C for 3 h. The clear, orange-red reaction mixture was then concentrated under reduced pressure and the residue was redissolved in dimethoxyethane (30 mL). The mixture was heated to 80°C for 3 h. The reaction mixture was cooled to rt, diluted with ethyl acetate (100 mL) and water (100 mL), and stirred for 15 minutes until almost all color was extracted into the organic layer. The layers were separated and the aqueous layer extracted with additional ethyl acetate (75 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (75 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford an orange oil. The crude product was

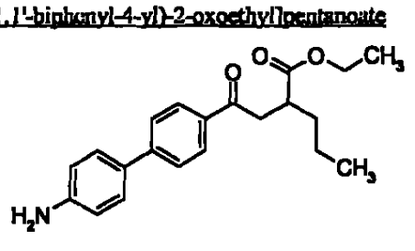
purified by flash chromatography (10:1 hexane:ethyl acetate) to afford ethyl 2-[2-(4-bromophenyl)-2-oxoethyl]pentanoate (1.33 g, 20%). LC-MS ret. time 3.60 min, *m/z* 326.05 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H), 1.25 (t, 3H), 1.29-1.43 (m, 2H), 1.57-1.73 (m, 2H), 2.90-3.08 (m, 2H), 3.34-3.47 (m, 2H), 4.15 (q, 2H), 7.59 (d, 4H), 7.82 (d, 2H).

[095] Ethyl 2-[2-(4'-nitro-1,1'-biphenyl-4-yl)-2-oxoethyl]pentanoate



[096] Step 3. To a 150 mL 3-neck flask fitted with a reflux condenser was added ethyl 2-[2-(4-bromophenyl)-2-oxoethyl]pentanoate (1.33 g, 4.10 mmol) and 4-nitro phenyl boronic acid (0.81 g, 4.9 mmol), dissolved in toluene (37 mL) and dioxane (10 mL), followed by addition of saturated aqueous sodium carbonate (11 mL). A thin-gauge needle was inserted into the bi-phasic mixture and the mixture was degassed with argon over 30 minutes, at which point 1,2-bis[(diphenylphosphino) ferrocene] dichloropalladium(II) (0.17 g, 0.20 mmol) was added, followed by 15 minutes of degassing. The mixture was heated to 85°C for 16 h. The very darkly colored reaction mixture was allowed to cool, and diluted with ethyl acetate (100 mL) and saturated aqueous sodium chloride solution (100 mL). The layers were separated, the aqueous layer extracted twice with ethyl acetate (50 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (75 mL), dried over anhydrous magnesium sulfate, and filtered *in vacuo* through 2 cm Celite®/2 cm silica. The filtrate was concentrated under reduced pressure, leaving a dark red-brown oil, that was purified by flash chromatography (10:1 hexane:ethyl acetate, then 7:1 hexane:ethyl acetate, then 4:1 hexane:ethyl acetate) to afford ethyl 2-[2-(4'-nitro-1,1'-biphenyl-4-yl)-2-oxoethyl]pentanoate (0.71 g, 48%). LC-MS ret. time 3.88 min, *m/z* 369.8 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H), 1.30 (t, 3H), 1.35-1.50 (m, 2H), 1.60-1.83 (m, 2H), 3.0-3.18 (m, 2H), 3.5 (dd, 1H), 4.20 (q, 2H), 7.65-7.88 (overlapping d, 4H), 8.10 (d, 2H), 8.35 (d, 2H).

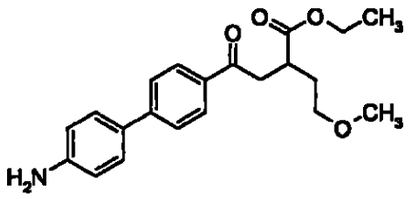
[097] Ethyl 2-[2-(4'-amino-1,1'-biphenyl-4-yl)-2-oxoethyl]pentanoate



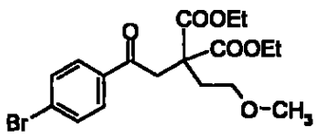
[098] Step 4. To a 100 mL flask fitted with a reflux condenser was added ethyl 2-[2-(4'-nitro-1,1'-biphenyl-4-yl)-2-oxoethyl]pentanoate (0.71 g, 1.9 mmol) dissolved in 85% aqueous ethanol (24 mL), followed by addition of 2 N aqueous hydrochloric acid solution (0.95 mL) and finely powdered iron (0) (1.10 g, 19.1 mmol), and the reaction mixture heated to 85°C over 2 h. Upon cooling, the darkly colored reaction mixture was filtered *in vacuo* through 2 cm Celite®/2 cm silica, resulting in all iron particulates/baseline material being removed. The yellow filtrate was concentrated under reduced pressure, resulting in a solid that was triturated in 20 mL diethyl ether/20 mL hexane, affording methyl 2-[2-(4'-amino-1,1'-biphenyl-4-yl)-2-oxoethyl]pentanoate as a tan solid (0.56 g, 88%). LC-MS ret. time 2.82 min, *m/z* 340.4 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H), 1.13 (t, 3H), 1.25-1.40 (m, 2H), 1.44-1.64 (m, 2H), 2.78-2.90 (m, 1H), 3.06-3.40 (m, 2H), 3.95-4.10 (m, 2H), 5.30-5.64 (br s, 1H), 6.65 (d, 2H), 7.46 (d, 2H), 7.67 (d, 2H), 7.93 (d, 2H).

[099] **Intermediate D**

Ethyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2-(2-methoxyethyl)-4-oxobutanoate



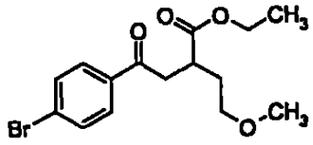
[100] Diethyl 2-[2-(4-bromophenyl)-2-oxoethyl]-2-(2-methoxyethyl)malonate



[101] Step 1. In a 100 mL flask was added sodium hydride (95%, 0.25 g, 10.1 mmol) followed by tetrahydrofuran (5 mL). The suspension was cooled to 0°C, and a solution of diethyl (2-methoxyethyl)-malonate (2.0 g, 9.16 mmol) in tetrahydrofuran (10 mL) was added dropwise over 10 minutes. The cooling bath was removed, and the reaction mixture was allowed to warm to rt over 45 minutes. A solution of 2,4'-bromoacetophenone (2.55 g, 19.6 mmol) in tetrahydrofuran (15 mL) was added via addition funnel over 10 minutes, and the resulting orange-red reaction mixture was stirred at rt for 16 h. The reaction mixture was slowly poured into 1 N aqueous hydrochloric acid solution (50 mL) with cooling at 0°C, and stirred for 15 minutes. Ethyl acetate (75 mL) and water (75 mL) were added, and the layers were separated. The aqueous layer was extracted with additional ethyl acetate (50 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (75 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated *in vacuo* to yield 3.7 g of a yellow oil. This oil was purified by flash chromatography

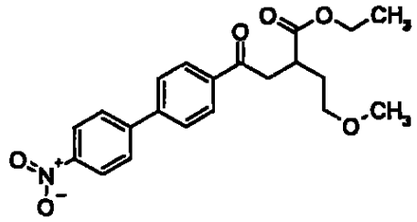
(10:1 hexane/ethyl acetate, then 4:1 hexane/ethyl acetate) to afford diethyl 2-[2-(4-bromophenyl)-2-oxoethyl]-2-(2-methoxyethyl)malonate (1.59 g, 42%). LC-MS ret. time 3.40 min, *m/z* 415 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 6H), 2.38 (t, 2H), 3.09 (s, 3H), 3.40 (t, 2H), 3.74 (s, 2H), 4.19 (q, 4H), 7.60 (d, 2H), 7.83 (d, 2H).

[102] Ethyl 4-(4-bromophenyl)-2-(2-methoxyethyl)-4-oxobutanoate



[103] Step 2. To a 150 mL flask was added diethyl 2-[2-(4-bromophenyl)-2-oxoethyl]-2-(2-methoxyethyl)malonate (1.59 g, 3.59 mmol) dissolved in acetone (16 mL) and ethanol (16 mL), followed by addition of 1N aqueous sodium hydroxide solution (3.6 mL). The reaction mixture was then heated at 55°C for 3 h. The reaction mixture was concentrated *in vacuo* to remove solvents, the residue redissolved in dimethoxyethane (32 mL), and the reaction mixture heated at 80°C for 3 h. The reaction mixture was cooled to rt, diluted with ethyl acetate (50 mL) and water (50 mL), and stirred for 15 minutes until almost all color was extracted into the organic layer. The layers were separated, the aqueous layer was extracted with additional ethyl acetate (50 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*, to afford ethyl 4-(4-bromophenyl)-2-(2-methoxyethyl)-4-oxobutanoate (1.06 g, 86%). No further purification of this material was required. LC-MS ret. time 3.18 min, *m/z* 342.8 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, 3H), 1.77-1.92 (m, 1H), 1.94-2.10 (m, 1H), 3.05-3.2 (m, 2H), 3.35-3.50 (m, 3H), 4.09-4.25 (m, 2H), 7.60 (d, 2H), 7.83 (d, 2H).

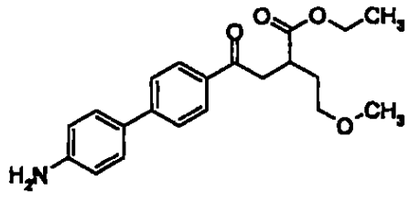
[104] Ethyl 2-(2-methoxyethyl)-4-(4'-nitro-1,1'-biphenyl-4-yl)-4-oxobutanoate



[105] Step 3. To a 150 mL 3-neck flask fitted with a reflux condenser was added ethyl 4-(4-bromophenyl)-2-(2-methoxyethyl)-4-oxobutanoate (1.06 g, 3.09 mmol) and 4-nitro-phenyl boronic acid (0.62 g, 3.70 mmol) dissolved in toluene (30 mL) and dioxane (8.50 mL), followed by addition of saturated aqueous sodium carbonate solution (8.50 mL). A thin-gauge needle was inserted into the bi-phasic mixture and degassed with argon over 30 minutes, at which point 1,2-bis[(diphenylphosphino) ferrocene] dichloropalladium(II) (0.13 g, 0.15 mmol) was added, followed by an additional

15 minutes of degassing. The reaction mixture was heated at 85°C for 16 h, and then the resulting dark-colored reaction mixture was allowed to cool, and was diluted with ethyl acetate (75 mL) and saturated aqueous sodium chloride solution (75 mL). The layers were separated, the aqueous layer was extracted twice with ethyl acetate (50 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (75 mL), dried over anhydrous magnesium sulfate, and filtered *in vacuo* through 2 cm Celite®/ 2 cm silica. The filtrate was concentrated *in vacuo*, leaving a dark red-brown oil, that was purified by flash chromatography (4:1 hexane/ethyl acetate, then 3:1 hexane/ethyl acetate, then 2:1 hexane/ethyl acetate) to afford ethyl 2-(2-methoxyethyl)-4-(4'-nitro-1,1'-biphenyl-4-yl)-4-oxobutanoate (1.04 g ,88%). LC-MS ret. time 3.38 min, *m/z* 385.9 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3H), 1.80-1.95 (m, 1H), 1.95-2.10 (m, 1H), 3.10-3.25 (m, 2H), 3.40-3.58 (m, 3H), 4.17 (q, 2H), 7.67-7.82 (2d, 4H), 8.10 (d, 2H), 8.33 (d, 2H).

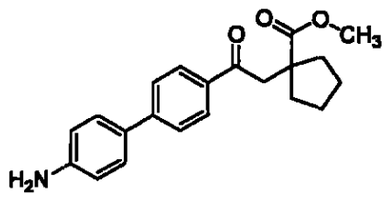
[106] Ethyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2-(2-methoxyethyl)-4-oxobutanoate



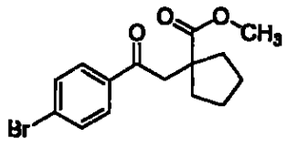
[107] Step 4. To a 100 mL flask fitted with a reflux condenser was added ethyl 2-(2-methoxyethyl)-4-(4'-nitro-1,1'-biphenyl-4-yl)-4-oxobutanoate (1.04 g, 2.71 mmol) dissolved in 85% aqueous ethanol (24 mL), followed by addition of 2 N aqueous hydrochloric acid solution (1.35 mL) and finely powdered iron (0) (1.51 g, 27.1 mmol), and the reaction mixture was heated at 85°C for 2 h. Upon cooling, the darkly-colored reaction mixture was filtered *in vacuo* through 2 cm Celite®/2 cm silica, resulting in all iron particulates and polar material being removed. The yellow filtrate was concentrated *in vacuo*, resulting in a solid that was purified by flash chromatography (3:1 hexane/ethyl acetate) affording ethyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2-(2-methoxyethyl)-4-oxobutanoate as a tan solid (0.89g, 93%). LC-MS ret. time 2.33 min, *m/z* 356.2 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.18-1.33 (m, 3H), 1.79-2.10 (overlapping m, 2H), 3.10-3.21 (m, 2H), 3.30 (s, 3H), 3.48 (t, 3H), 4.16 (t, 3H), 7.15 (d, 2H), 7.55 (d, 2H), 7.62 (d, 2H), 8.03 (d, 2H).

[108] **Intermediate E**

Methyl 1-[2-(4'-amino-1,1'-biphenyl-4-yl)-2-oxoethyl]cyclopentanecarboxylate

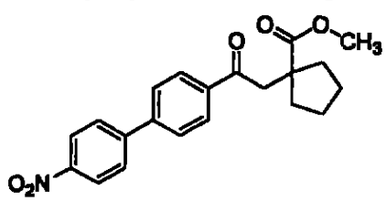


[109] Methyl 1-[2-(4-bromophenyl)-2-oxoethyl]cyclopentanecarboxylate



[110] Step 1. To a 150 mL flask was added dichloromethane (70 mL), methyl 1-(2-chloro-2-oxoethyl)cyclopentanecarboxylate] (3.50 g, 16.8 mmol) [prepared as described by Bajaj, et al., J. Indian Chem. Soc. 52:1076-78, 1975] and bromobenzene (2.77 g, 17.6 mmol), and the reaction mixture cooled to 0°C before aluminum trichloride (4.77 g, 35.7 mmol) was slowly added. The mixture was stirred for 1 h at 0°C, then for 12 h at rt. The reaction mixture was slowly poured into 50 mL chilled (0°C) 1 N aqueous hydrochloric acid solution. Water (50 mL) was added, followed by ethyl acetate (100 mL), and the mixture stirred for 30 minutes. The layers were separated and the aqueous layer extracted with additional ethyl acetate (100 mL). The combined organic layer was washed with saturated aqueous sodium chloride (100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield a brown oil which was purified by flash chromatography (10:1/hexane: ethyl acetate) to afford methyl 1-[2-(4-bromophenyl)-2-oxoethyl] cyclopentane carboxylate as a yellow, crystalline solid (1.62 g, 30%). LC-MS ret. time 3.45 min, *m/z* 324.8 (MH^+); ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.50-1.83 (overlapping signals, 6H), 2.22-2.33 (m, 2H), 3.37 (s, 2H), 3.66 (s, 3H), 7.59 (d, 2H), 7.80 (d, 2H).

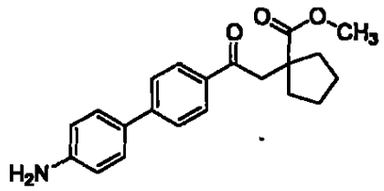
[111] Methyl 1-[2-(4'-nitro-1,1'-biphenyl-4-yl)-2-oxoethyl]cyclopentanecarboxylate



[112] Step 2. To a 150 mL 3-neck flask fitted with a reflux condenser was added methyl 1-[2-(4-bromophenyl)-2-oxoethyl]cyclopentanecarboxylate (1.58 g, 4.64 mmol), 4-nitro phenyl boronic acid (0.93 g, 5.6 mmol), toluene (45 mL), and dioxane (13 mL), followed by the addition of a saturated aqueous sodium carbonate solution (13 mL). The mixture was degassed using argon and 1,2-

bis[(diphenylphosphino) ferrocene] dichloropalladium(II) (0.19 g, 0.23 mmol) was added, followed by an additional 15 minutes of degassing, and the deep red reaction mixture was heated to 85°C for 16 h. The very darkly colored reaction mixture was allowed to cool, and then was diluted with ethyl acetate (100 mL) and saturated aqueous sodium chloride solution (100 mL). The layers were separated and the aqueous layer was extracted twice with ethyl acetate (50 mL). The combined organic layer was washed with saturated aqueous sodium chloride solution (100 mL), dried over anhydrous magnesium sulfate, and filtered under reduced pressure through 2 cm Celite®/2 cm silica. The filtrate was concentrated under reduced pressure, leaving a dark red-brown oil, that was purified by flash chromatography (4:1/hexane: ethyl acetate, then 3:1/hexane: ethyl acetate, then 2:1/hexane: ethyl acetate) to afford methyl 1-[2-(4'-nitro-1,1'-biphenyl-4-yl)-2-oxoethyl]cyclopentanecarboxylate (1.65 g, 93 %). LC-MS ret. time 3.56 min, *m/z* 368.0 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.56-1.85 (overlapping signals, 6H), 2.23-2.37 (m, 2H), 3.45 (s, 2H), 3.67 (s, 3H), 7.70 (d, 2H), 7.77 (d, 2H), 8.06 (d, 2H), 8.34 (d, 2H).

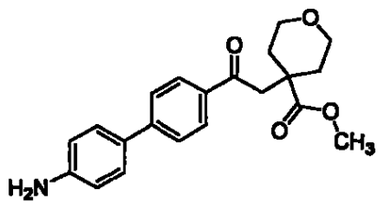
[113] Methyl 1-[2-(4'-amino-1,1'-biphenyl-4-yl)-2-oxoethyl]cyclopentanecarboxylate



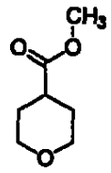
[114] Step 3. To a 100 mL flask fitted with a reflux condenser was added methyl 1-[2-(4'-nitro-1,1'-biphenyl-4-yl)-2-oxoethyl]cyclopentanecarboxylate (1.68 g, 4.40 mmol) dissolved in 85% aqueous ethanol (55 mL), followed by addition of 2 N aqueous hydrochloric acid solution (2.20 mL) and finely powdered iron (0) (2.46 g, 44.1 mmol). The reaction mixture was heated to 85°C over 2 h. Upon cooling, the darkly-colored reaction mixture was filtered under reduced pressure through 2 cm Celite®/ 2 cm silica, in order to remove iron particulates and polar impurities. The yellow filtrate was concentrated under reduced pressure, resulting in a solid that was triturated with 20 mL diethyl ether/20 mL hexane to afford methyl 1-[2-(4'-amino-1,1'-biphenyl-4-yl)-2-oxoethyl] cyclopentanecarboxylate as a light tan solid (1.20 g, 76 %). LC-MS ret. time 2.71 min, *m/z* 338.1 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.55-1.84 (overlapping signals, 6H), 2.25-2.35 (m, 2 H), 3.44 (s, 2H), 3.67 (s, 3H), 7.40-8.10 (overlapping signals, 8H).

[115] Intermediate F

Methyl 4-[2-(4'-amino-1,1'-biphenyl-4-yl)-2-oxoethyl]tetrahydro-2H-pyran-4-carboxylate

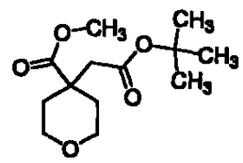


[116] Methyl tetrahydro-2H-pyran-4-carboxylate



[117] Step 1. Tetrahydro-2H-pyran-4-carboxylic acid (1.00 g, 7.68 mmol) was slowly added to a stirred suspension of anhydrous potassium carbonate (1.17 g, 8.45 mmol) in acetone (40 mL), followed by dimethyl sulfate (0.8 mL, 8.45 mmol). The mixture was stirred and heated for 3 h. The inorganic salts were then removed by filtration and washed with acetone, and the filtrate was dried and concentrated to give methyl tetrahydro-2H-pyran-4-carboxylate (1.1 g, 99%), which was used in the next step without further purification. GC-MS *m/z* 145 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 11.70-1.80 (m, 4H), 2.47-2.52 (m, 1H), 3.34-3.43 (m, 2H), 3.65 (s, 3H), 3.88-3.95 (m, 2H).

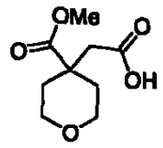
[118] Methyl 4-(2-*tert*-butoxy-2-oxoethyl)tetrahydro-2H-pyran-4-carboxylate



[119] Step 2. Diisopropylamine (1.28 mL, 9.16 mmol) was diluted with tetrahydrofuran (2 mL) and cooled to -78°C. *n*-Butyllithium (2.5 M, 3.66 mL, 9.16 mmol) was added dropwise, and the solution was allowed to stir for 1 h. Methyl tetrahydro-2H-pyran-4-carboxylate (1.1 g, 7.63 mmol) was added as a solution in tetrahydrofuran (1.5 mL) at -78°C. The mixture was allowed to warm to -35°C and stirred for 1 h. *tert*-Butyl bromoacetate (1.58 mL, 10.7 mmol) was added neat at -35°C. The mixture was allowed to warm to 0°C and stirred for 2 h. The mixture was stirred at rt overnight. Water was added at 0°C and the mixture extracted with ethyl acetate. The organic phase was washed with brine, and dried over sodium sulfate. The crude product was purified by flash chromatography (Biotage Flash 40M, 6:1 hexane/ethyl acetate) to afford methyl 4-(2-*tert*-butoxy-2-oxoethyl)tetrahydro-2H-pyran-4-carboxylate (1.12 g, 56%). LC-MS ret. time 2.47 min, *m/z* 258.7 (MH^+); ^1H NMR (300

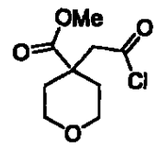
MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.52-1.61 (m, 2H), 2.00-2.07 (m, 2H), 2.50 (s, 2H), 3.52-3.60 (m, 2H), 3.70 (s, 3H), 3.71-3.77 (m, 2H).

[120] [4-(Methoxycarbonyl)tetrahydro-2H-pyran-4-yl]acetic acid



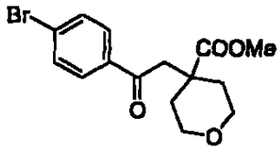
[121] Step 3. To a solution of methyl 4-(2-*tert*-butoxy-2-oxoethyl)tetrahydro-2H-pyran-4-carboxylate (1.1 g, 4.26 mmol) in dichloromethane (5.0 mL) was added trifluoroacetic acid (5.0 mL) and the resulting solution was stirred at rt for 5 h. The mixture was concentrated under reduced pressure to afford [4-(methoxycarbonyl)tetrahydro-2H-pyran-4-yl]acetic acid (900 mg, 94%), which was used in the next step without further purification. LC-MS ret. time 0.93 min, *m/z* 202.9 (MH^+); ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.70 (m, 2H), 2.10-2.15 (m, 2H), 2.68 (s, 2H), 3.62-3.71 (m, 2H), 3.72 (s, 3H), 3.79-3.86 (m, 2H).

[122] Methyl 4-(2-chloro-2-oxoethyl)tetrahydro-2H-pyran-4-carboxylate



[123] Step 4. Thionyl chloride (20 mL) was added to [4-(methoxycarbonyl)tetrahydro-2H-pyran-4-yl]acetic acid (970 mg, 4.80 mmol) and the solution was stirred at rt for 3 h. The solvent was then removed and mixture was azeotroped with dichloromethane three times to afford methyl 4-(2-chloro-2-oxoethyl)tetrahydro-2H-pyran-4-carboxylate (1.05 g, 99%), which was used without purification in the next step.

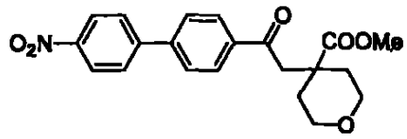
[124] Methyl 4-[2-(4-bromophenyl)-2-oxoethyl]tetrahydro-2H-pyran-4-carboxylate



[125] Step 5. To a solution of methyl 4-(2-chloro-2-oxoethyl)tetrahydro-2H-pyran-4-carboxylate (1.06 g, 4.8 mmol) and bromobenzene (1.13 g, 7.21 mmol) in dichloromethane (20 mL) at 0°C was added aluminum chloride (1.92 g, 14.4 mmol). The ice-water bath was removed and the reaction mixture was stirred at rt for 16 h. The mixture was then cooled at 0°C and quenched by the addition of 1 N HCl solution and water. The mixture was extracted with dichloromethane, and the combined

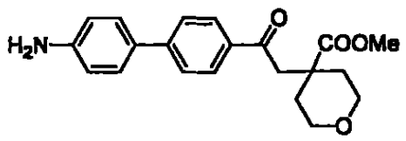
organic phases were dried over sodium sulfate. The crude material was then purified by flash chromatography (Biotage Flash 40 M, 2:1 hexane/ethyl acetate, to afford methyl 4-[2-(4-bromophenyl)-2-oxoethyl]tetrahydro-2H-pyran-4-carboxylate (900 mg, 55%). LC-MS ret. time 2.76 min; *m/z* 342.9 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.58-1.69 (m,. 2H), 2.12-2.18 (m, 2H), 3.28 (s, 2H), 3.64 (s, 3H), 3.69-3.77 (m, 4H), 7.59 (d, 2H), 7.77 (d, 2H).

[126] Methyl 4-[2-(4'-nitro-1,1'-biphenyl-4-yl)-2-oxoethyl]tetrahydro-2H-pyran-4-carboxylate



[127] Step 6. Methyl 4-[2-(4-bromophenyl)-2-oxoethyl]tetrahydro-2H-pyran-4-carboxylate (820 mg, 2.40 mmol) and 4-nitrophenyl boronic acid (481 mg, 2.88 mmol) were combined in a dry flask under argon. Toluene (20 mL) and dioxane (5 mL) were added, and the resulting solution was degassed for 30 minutes by a flow of argon. The degassing was continued during the addition of saturated aqueous sodium carbonate (6 mL) and [1,1'-bis(diphenylphosphino)-ferrocene]dichloro palladium(II), 1:1 complex with dichloromethane (98 mg, 0.12 mmol). The resulting mixture was then heated at 85°C for 16 h before it was cooled to rt. Water was added, and the aqueous layer was extracted twice with ethyl acetate. The combined organic phases were then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (Biotage Flash 40) using 1:1 ethyl acetate/hexane to afford methyl 4-[2-(4'-nitro-1,1'-biphenyl-4-yl)-2-oxoethyl]tetrahydro-2H-pyran-4-carboxylate (730 mg, 79%). LC-MS ret. time 3.03; *m/z* 383.9 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-1.73 (m, 2H), 2.17-2.21 (m, 2H), 3.37 (s, 2H), 3.68 (s, 3H), 3.71-3.78 (m, 4H), 7.70 (d, 2H), 7.77 (d, 2H), 8.02 (d, 2H), 8.31 (d, 2H).

[128] Methyl 4-[2-(4'-amino-1,1'-biphenyl-4-yl)-2-oxoethyl]tetrahydro-2H-pyran-4-carboxylate

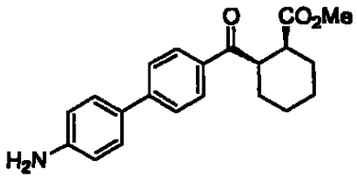


[129] Step 7. To a solution of methyl 4-[2-(4'-nitro-1,1'-biphenyl-4-yl)-2-oxoethyl]tetrahydro-2H-pyran-4-carboxylate (1.24 g, 3.25 mmol) in 85% ethanol (50 mL) was added iron powder (1.81 g), followed by 2 N aqueous HCl (1.62 mL), and the resulting mixture was refluxed for 2.5 h. The mixture was then filtered through a pad of Celite® and the filtrate was extracted with dichloromethane. The combined organic phases were then dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford methyl 4-[2-(4'-amino-1,1'-biphenyl-4-yl)-2-oxoethyl]tetrahydro-2H-pyran-4-carboxylate (1.05 g, 91%). LC-MS ret. time 2.20; *m/z* 354.0 (MH^+); ^1H NMR (300 MHz,

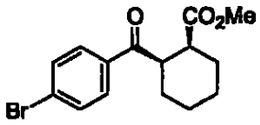
$CDCl_3$) δ 1.57-1.66 (m, 2H), 2.09 (m, 2H), 3.28 (s, 2H), 3.61 (s, 3H), 3.64-3.71 (m, 4H), 6.76 (d, 2H), 7.42 (d, 2H), 7.54 (d, 2H), 7.88 (d, 2H).

[130] **Intermediate G**

Methyl *cis*-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]cyclohexanecarboxylate

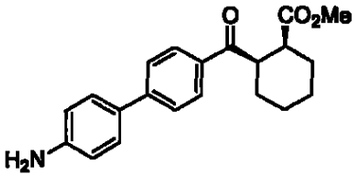


[131] Methyl *cis*-2-(4-bromobenzoyl)cyclohexanecarboxylate



[132] Step 1. To a solution of *cis*-2-(4-bromobenzoyl)-1-cyclohexanecarboxylic acid (4.0 g, 12.85 mmol) in MeOH (50 mL) was added 2,2-dimethoxypropane (2.01 g, 19.28 mmol) and HCl (4.0 M in dioxane, 1.20 mL). The resulting solution was stirred at 40°C for 3 days, and then evaporated to dryness. The resulting residue was purified by flash chromatography (Biotage Flash 40M) using 3 to 6% ethyl acetate in hexanes to afford methyl *cis*-2-(4-bromobenzoyl)cyclohexanecarboxylate (1.76 g, 42%). LC-MS ret. time 3.40; *m/z* 326 (MH^+); ^1H NMR (400 MHz, CD_2Cl_2) δ 1.35-1.51 (m, 3H), 1.72-1.86 (m, 2H), 1.91-2.05 (m, 2H), 2.11-2.20 (m, 1H), 2.74 (m, 1H), 3.58 (s, 3H), 3.82 (q, 1H), 7.62 (m, 2H), 7.73 (m, 2H).

[133] Methyl *cis*-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]cyclohexanecarboxylate

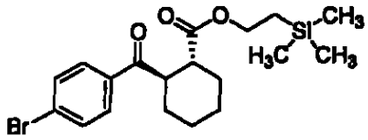


[134] Step 2. Methyl *cis*-2-(4-bromobenzoyl)cyclohexanecarboxylate (1.76 g, 5.41 mmol) and 4-amino phenyl boronic acid (1.13 g, 6.49 mmol) were added to a clean dry flask under argon. Toluene (50 mL), EtOH (20 mL), and 3 M aqueous Na_2CO_3 (14 mL, 43 mmol) were added, and resulting solution was degassed for 30 minutes by using a flow of argon. Then [1,1'-bis(diphenylphosphino)-ferrocene]dichloro palladium(II), 1:1 complex with dichloromethane (442 mg, 0.54 mmol) was added and the resulting mixture was heated at 85°C for 16 h. The mixture was cooled to rt, and then diluted with EtOAc and passed through a Celite® pad. The solvent was removed by rotary evaporation. Water and EtOAc were added, and the aqueous layer was

extracted with EtOAc. The combined organic phases were washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Biotage Flash 40M) using 33 to 40% ethyl acetate in hexane to afford methyl *cis*-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]cyclohexanecarboxylate.(1.54 g, 84%). LC-MS ret. time 3.99; *m/z* 338 (MH^+);^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.37-1.53 (m, 3H), 1.74-1.88 (m, 2H), 1.90-1.99 (m, 1H), 2.04-2.22 (m, 2H), 2.75 (m, 1H), 3.59 (s, 3H), 3.90 (q, 1H), 6.79 (m, 2H), 7.48 (m, 2H), 7.63 (m, 2H), 7.89 (m, 2H).

[135] **Intermediate H**

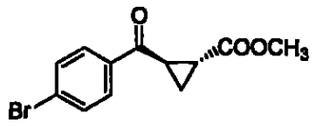
***trans*-(Trimethylsilyl)ethyl 2-(4-bromobenzoyl)cyclohexanecarboxylate**



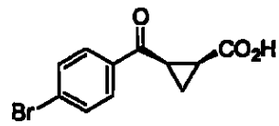
[136] To a solution of *trans*-2-(4-bromobenzoyl)cyclohexanecarboxylic acid (5.0 g, 16.07 mmol) in DCM (80 mL) was added 2-(trimethylsilyl)ethanol (2.1 g, 17.68mmol), *N,N'*-dimethylamino-pyridine (98 mg, 0.80 mmol), and EDCI (4.0 g, 20.89 mmol). The resulting reaction mixture was stirred at rt for 2 days. Water was added, and the mixture was diluted with DCM. The aqueous layer was separated and extracted with DCM. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Silica gel chromatography (Biotage cartridge), eluting with 10% EtOAc in hexane gave *trans*-(trimethylsilyl)ethyl 2-(4-bromobenzoyl)cyclohexanecarboxylate (2.44 g, 37%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ -0.01 (s, 9H), 0.85 (m, 2H), 1.45 (m, 3H), 1.73 (m, 2H), 1.90 (m, 2H), 2.18 (m, 1H), 2.71 (m, 1H), 3.80 (m, 1H), 4.05 (m, 2H), 7.58 (d, 2H), 7.70 (d, 2H).

[137] **Intermediate I**

Methyl *trans*-2-(4-bromobenzoyl)cyclopropanecarboxylate



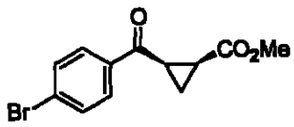
[138] *cis*-2-(4-Bromobenzoyl)cyclopropanecarboxylic acid



[139] Step 1. To a cold (0°C) stirred solution of bromobenzene (9.09 g, 57.89 mmol) and $AlCl_3$ (18.36 g, 137.84 mmol) in dry DCM (150 mL) was added 3-oxabicyclo[3.1.0]hexane-2,4-dione (5.40 g, 48.24 mmol). The reaction mixture was stirred at rt for 3 days. The dark-red solution was then

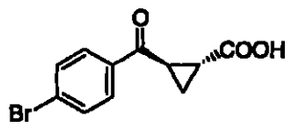
poured into ice-cold water (120 mL), and conc. HCl (10 mL) was added. The solution was stirred for few minutes, and the layers were separated. The aqueous layer was extracted with DCM and the combined organic phases were washed with water, brine, dried over Na_2SO_4 and concentrated to give *cis*-2-(4-bromobenzoyl)cyclopropanecarboxylic acid (9.69 g, 65%). LC-MS ret. time 2.50; *m/z* 270 (MH^+); ^1H NMR (400 MHz, CD_2Cl_2) δ 1.54 (m, 1H), 1.85 (m, 1H), 2.37 (m, 1H), 2.88 (m, 1H), 7.65 (m, 2H), 7.90 (m, 2H).

[140] Methyl *cis*-2-(4-bromobenzoyl)cyclopropanecarboxylate



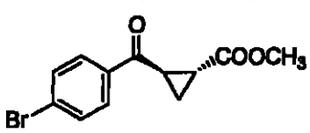
[141] Step 2. To a solution of *cis*-2-(4-bromobenzoyl)cyclopropanecarboxylic acid (10.6 g, 36.63 mmol) in MeOH (250 mL) was added 2,2-dimethoxypropane (9.54 g, 91.59 mmol) and HCl (4.0 M in dioxane, 3.50 mL). The resulting solution was stirred at 40°C for 3 days, and then evaporated to dryness. The resulting residue was purified by flash chromatography (Biotage Flash 40M) using 15 to 25% ethyl acetate in hexanes to afford methyl *cis*-2-(4-bromobenzoyl)-cyclopropanecarboxylate (10.34 g, 99%). ^1H NMR (400 MHz, CD_2Cl_2) δ 1.39 (m, 1H), 1.82 (m, 1H), 2.34 (m, 1H), 2.77 (m, 1H), 3.54 (s, 3H), 7.65 (m, 2H), 7.89 (m, 2H).

[142] *trans*-2-(4-Bromobenzoyl)cyclopropanecarboxylic acid.



[143] Step 3. Methyl *cis*-2-(4-bromobenzoyl)cyclopropanecarboxylate (10.34 g, 36.52 mmol) was dissolved in MeOH (100 mL), and then 15 mL 50% aqueous NaOH solution was added. The reaction mixture was stirred at 40°C for 3 days. Solvent was removed by rotary evaporation and the residue was dissolved in water. Concentrated HCl was added to adjust the acidity to pH 1. The precipitate that formed was collected by filtration and dried in a vacuum oven overnight to give *trans*-2-(4-bromobenzoyl)cyclopropanecarboxylic acid (9.43 g, 95%). LC-MS ret. time 2.51, *m/z* 270 (MH^+); ^1H NMR (400 MHz, CD_2Cl_2) δ 1.68 (m, 2H), 2.38 (m, 1H), 3.22 (m, 1H), 7.67 (m, 2H), 7.90 (m, 2H).

[144] Methyl *trans*-2-(4-bromobenzoyl)cyclopropanecarboxylate.

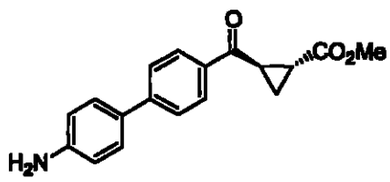


[145] Step 4. To a solution of *trans*-2-(4-bromobenzoyl)cyclopropanecarboxylic acid (9.43 g, 32.59 mmol) in MeOH (200 mL) was added 2,2-dimethoxypropane (10.18 g, 97.77 mmol) and HCl

(4.0 M in dioxane, 4.0 mL). The resulting solution was stirred at 40°C overnight, and then evaporated to dryness. The resulting residue was purified by flash chromatography (Biotage Flash 40M) using 15 to 25% ethyl acetate in hexanes to afford methyl *trans*-2-(4-bromobenzoyl)cyclopropanecarboxylate (7.7 g, 83%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.68 (m, 2H), 2.37 (m, 1H), 3.21 (m, 1H), 3.65 (s, 3H), 7.68 (m, 2H), 7.90 (m, 2H).

[146] **Intermediate J**

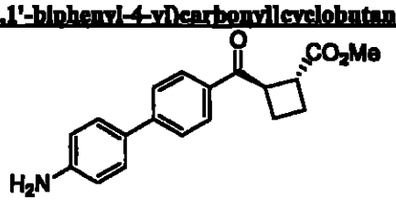
Methyl *trans*-2-[(4'-amino-1, 1'-biphenyl-4-yl) carbonyl]cyclopropanecarboxylate



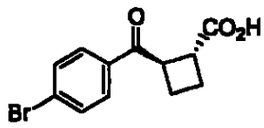
[147] Methyl *trans*-2-(4-bromobenzoyl)cyclopropanecarboxylate (1.33 g, 4.70 mmol) and 4-aminophenyl boronic acid (0.98 g, 5.64 mmol) were combined in a dry flask under argon. Toluene (25 mL), EtOH (10 mL), and 3 M aqueous Na_2CO_3 (7 mL, 20 mmol) were added, and the resulting solution was degassed for 30 minutes by using a flow of argon. Then [1,1'-bis(diphenylphosphino)-ferrocene]dichloro palladium(II), 1:1 complex with dichloromethane (383 mg, 0.47 mmol) was added, and the resulting mixture was heated at 85°C for 16 h. The mixture was cooled to rt, then diluted with EtOAc and passed through a Celite® pad. The solvent was removed by rotary evaporation. Water and EtOAc were added, and the aqueous layer was extracted with EtOAc. The combined organic phases were washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Biotage Flash 40M) using 33 to 40% ethyl acetate in hexane to afford methyl *trans*-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]-cyclopropanecarboxylate (0.92 g, 66%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.60 (m, 2H), 2.35 (m, 1H), 3.22 (m, 1H), 3.73 (s, 3H), 6.80 (m, 2H), 7.51 (m, 2H), 7.68 (m, 2H), 8.05 (m, 2H).

[148] **Intermediate K**

Methyl *trans*-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]cyclobutanecarboxylate

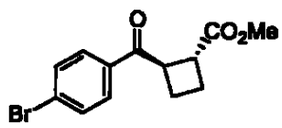


[149] *trans*-2-(4-Bromobenzoyl)cyclobutanecarboxylic acid



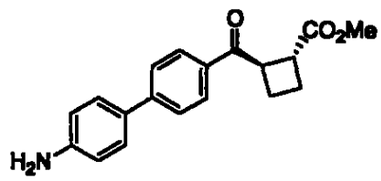
[150] Step 1. To a cold (0°C) stirred solution of bromobenzene (10.98 g, 69.94 mmol) and $AlCl_3$ (19.41 g, 145.71 mmol) in dry DCM (150 mL) was added cyclobutane dicarboxylic anhydride (7.35 g, 58.28 mmol). The reaction mixture was stirred at rt for 3 days. The dark-red solution was then poured into ice-cold water (120 mL), and conc. HCl (10 mL) was added. The solution was stirred for a few minutes, the aqueous layer was extracted with DCM, and then the combined organic phases were extracted with 1 N aqueous NaOH. The aqueous layer was stirred at rt overnight. The solution was acidified by addition of conc. HCl to pH 1.5, extracted with EtOAc, and the combined organic phases were washed with water, brine, dried over Na_2SO_4 and concentrated to give *trans*-2-(4-bromobenzoyl)cyclobutanecarboxylic acid (8.20 g, 49). ^1H NMR (400 MHz, CD_2Cl_2) δ 2.20-2.44 (m, 4H), 3.67 (m, 1H), 4.21 (m, 1H), 7.64 (m, 2H), 7.80 (m, 2H).

[151] Methyl *trans*-2-(4-bromobenzoyl)cyclobutanecarboxylate



[152] Step 2. To a solution of *trans*-2-(4-bromobenzoyl)cyclobutanecarboxylic acid (8.2 g, 28.94 mmol) in MeOH (250 mL) was added 2,2-dimethoxypropane (3.65 g, 35.02 mmol) and HCl (4.0 M in dioxane) (2.0 mL). The resulting solution was stirred at rt for 3 days, and then evaporated to dryness. The resulting residue was purified with flash chromatography (Biotage Flash 40M) using 4 to 11% ethyl acetate in hexanes to afford methyl *trans*-2-(4-bromobenzoyl)cyclobutanecarboxylate (6.21 g, 78%). ^1H NMR (400 MHz, CD_2Cl_2) δ 2.14-2.39 (m, 4H), 3.62 (m, 1H), 3.68 (s, 3H), 4.24 (m, 1H), 7.63 (m, 2H), 7.80 (m, 2H).

[153] Methyl *trans*-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]cyclobutanecarboxylate

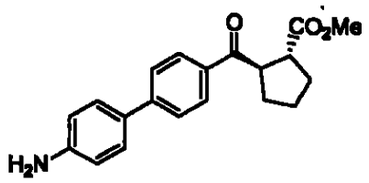


[154] Step 3. Methyl *trans*-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]cyclobutanecarboxylate (1.25 g, 4.21 mmol) and 4-aminophenyl boronic acid (0.88 g, 5.05 mmol) were combined in a dry flask under argon. Toluene (25 mL), EtOH (10 mL), and 3 M aqueous Na_2CO_3 (5.0 mL, 15 mmol) were added, and the resulting solution was degassed for 30 minutes by using a flow of argon. Then [1,1'-

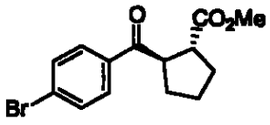
bis(diphenylphosphino)-ferrocene]dichloro palladium(II), 1:1 complex with dichloromethane (343 mg, 0.42 mmol), was added and the resulting mixture was heated at 85°C for 16 h. The mixture was cooled to rt, diluted with EtOAc, and passed through a Celite® pad. The solvent was removed by rotary evaporation. Water and EtOAc were added, and the aqueous layer was extracted with EtOAc. The combined organic phases were washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Biotage Flash 40M) using 29 to 37% ethyl acetate in hexane to afford methyl *trans*-2-[(4'-amino-1,1'-biphenyl-4-yl)-carbonyl]cyclobutanecarboxylate (0.91 g, 70%). LC-MS ret. time 2.24; *m/z* 310.4 (MH^+); ^1H NMR (400 MHz, CD_2Cl_2) δ 2.13-2.36 (m, 4H), 3.60 (m, 1H), 3.64 (s, 1H), 4.24 (m, 1H), 6.73 (m, 2H), 7.43 (m, 2H), 7.59 (m, 2H), 7.88 (m, 2H).

[155] Intermediate L

Methyl *trans*-2-[(4'-amino-1, 1'-biphenyl-4-yl) carbonyl]cyclopentanecarboxylate

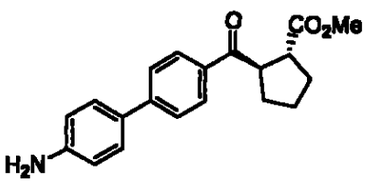


[156] Methyl *trans*-2-(4-bromobenzoyl)cyclopentanecarboxylate



[157] Step 1. To a solution of *trans*-2-(4-bromobenzoyl)cyclopentanecarboxylic acid (2.0 g, 6.26 mmol) in MeOH (70 mL) was added 2,2-dimethoxypropane (1.63 g, 15.65 mmol) and HCl (4.0 M in dioxane) (1.0 mL). The resulting solution was stirred at 40°C overnight and then evaporated to dryness. The resulting residue was purified by flash chromatography (Biotage Flash 40M) using 7 to 11% ethyl acetate in hexanes to afford methyl *trans*-2-(4-bromobenzoyl)cyclopentanecarboxylate (1.62 g, 83%). ^1H NMR (400 MHz, CD_2Cl_2) δ 1.70-1.95 (m, 4H), 2.08-2.21 (m, 2H), 3.40 (m, 1H), 3.64 (s, 3H), 4.04 (m, 1H), 7.64 (m, 2H), 7.86 (m, 2H).

[158] Methyl *trans*-2-[(4'-amino-1, 1'-biphenyl-4-yl)carbonyl]cyclopentanecarboxylate

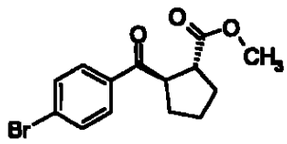


[159] Step 2. Methyl *trans*-2-(4-bromobenzoyl)cyclopentanecarboxylate (1.60 g, 5.14 mmol) and 4-aminophenyl boronic acid (1.07 g, 6.17 mmol) were combined in a dry flask under argon. Toluene

(25 mL), EtOH (10 mL), and 3 M aqueous Na_2CO_3 (8.50 mL, 25 mmol) were added and resulting solution was degassed for 30 minutes by using a flow of argon. Then [1,1'-bis(diphenylphosphino)-ferrocene]dichloro palladium(II), 1:1 complex with dichloromethane (419.9 mg, 0.51 mmol), was added and the resulting mixture was heated at 85°C for 16 h. The mixture was cooled to rt, diluted with EtOAc, and passed through a Celite® pad. The solvent was removed by rotary evaporation. Water and EtOAc were added and the aqueous layer was extracted with EtOAc. The combined organic phases were washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Biotage Flash 40M) using 29 to 33% ethyl acetate in hexane to afford methyl *trans*-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]-cyclopentanecarboxylate (1.12 g, 67%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.71-1.97 (m, 4H), 2.17 (m, 2H), 3.44 (m, 1H), 3.65 (s, 3H), 4.12 (m, 1H), 6.84 (m, 2H), 7.51 (m, 2H), 7.66 (m, 2H), 8.00 (m, 2H).

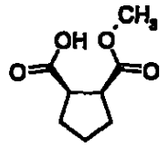
[160] **Intermediate M**

(*R,R*)-2-(4-Bromo-benzoyl)-cyclopentanecarboxylic acid methyl ester



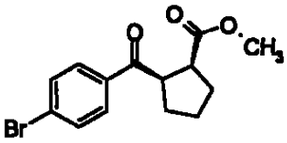
(R,R)

[161] (±)-Cyclopentane-1,2-dicarboxylic acid monomethyl ester



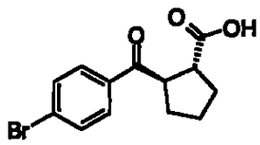
[162] Step 1. The anhydride tetrahydro-cyclopenta[c]furan-1,3-dione (50.0 g, 356.8 mmol, prepared as described by Wilkening, et al., Syn Comm. 14(3):227, 1984) was dissolved in methanol (250 mL), and the mixture was then heated at 50–55°C under N_2 for 5 h. NMR analysis showed no starting material remaining. Methanol was removed by rotary evaporation, and the residue was dried *in vacuo* to afford the desired product as a colorless oil (60.0 g, 98%). ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H), 3.08 (m, 2H), 2.04 (m, 4H), 1.90 (m, 1H), 1.65 (m, 1H).

[163] (±)-*cis*-2-(4-Bromo-benzoyl)-cyclopentanecarboxylic acid methyl ester



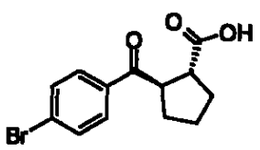
[164] Step 2. A solution of the monomethyl ester (92.0 g, 534.3 mmol), $SOCl_2$ (116.3 mL, 1.60 mol), and DMF (1 mL) in 850 mL CH_2Cl_2 was stirred at rt overnight under N_2. NMR analysis showed little starting material remaining. The solvent was removed by rotary evaporation at <40°C, and the residue was dried *in vacuo* for 1 h. This dried residue was dissolved in bromobenzene (337.6 mL, 3.2 mol), and $AlCl_3$ (142.5 g, 1.07 mol) was then added portionwise at <5°C. The reaction mixture turned dark brown, and was stirred at <5°C for 4 h under N_2. NMR analysis then showed little starting material remaining. The reaction mixture was then slowly poured *into* 2 L ice-water, and then 1 L EtOAc was added. After the mixture was stirred for 10 minutes, the aqueous (top) layer was separated, and extracted with 500 mL EtOAc. The combined organic layers were washed with water (2 x 1 L) and saturated $NaHCO_3$ solution (200 mL), and dried over Na_2SO_4. Removal of solvent and drying *in vacuo* provided 175.0 g (>95%) of the desired product. ^1H NMR ($CDCl_3$) δ 7.80 (d, 2H), 7.60 (d, 2H), 4.07 (m, 1H), 3.53 (s, 3H), 3.07 (m, 1H), 2.20 (m, 1H), 2.00 (m, 4H), 1.70 (m, 1H).

[165] (±)-*trans*-2-(4-Bromo-benzoyl)-cyclopentanecarboxylic acid



[166] Step 3. A solution of NaOH (128.2 g, 3.2 mol) in 700 mL water was added to a solution of *cis*-2-(4-bromo-benzoyl)-cyclopentanecarboxylic acid methyl ester (166.3 g, 534.3 mmol) in MeOH (700 mL). The reaction mixture was stirred at rt overnight. NMR analysis showed that little starting material remained. After ca. 1 L solvent was removed by rotary evaporation, the mixture was diluted with 1 L water. Conc. HCl was slowly added with stirring at <15°C, to adjust the acidity to pH <6. A precipitate formed, and stirring was continued for 1 h. The solid precipitate was filtered, and rinsed with water. The dried filter cake was dissolved in 1 L EtOAc, and dried over Na_2SO_4. Removal of solvent and drying *in vacuo* afforded the desired product (131 g, 83%). ^1H NMR ($CDCl_3$) δ 7.83 (d, 2H), 7.60 (d, 2H), 4.05 (m, 1H), 3.50 (m, 1H), 2.20 (m, 2H), 2.00 (m, 1H), 1.78 (m, 3H).

[167] (*R,R*)-*trans*-2-(4-Bromo-benzoyl)-cyclopentanecarboxylic acid

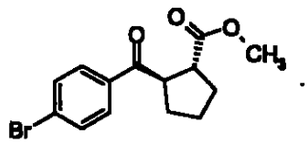


(R,R)

[168] Step 4. A mixture of (±)-*trans*-2-(4-bromo-benzoyl)-cyclopentanecarboxylic acid (114.3 g, 384.7 mmol) and (*R*)-(+)-alpha-methyl-benzylamine (23.3 g, 192.3 mmol) in CH_3CN (1125 mL) was heated at 90-95°C under N_2 to provide a solution. The hot solution was allowed to cool slowly with slow stirring overnight. The crystallized solid was filtered, and rinsed with CH_3CN (50 mL). Drying

in vacuo to a constant weight afforded 64.5 g of white solid (56% ee, by chiral HPLC). This solid was then dissolved in a mixture of solvents (258 mL EtOH and 516 mL water) with heating at 90–95°C under N_2. The hot solution was allowed to cool slowly with slow stirring overnight. The solid formed was filtered, and rinsed with 60 mL of 1:2 EtOH/water. After drying *in vacuo* to a constant weight, this white solid was stirred with 1 N HCl (500 mL) and EtOAc (500 mL) for 10 minutes. The organic layer was separated, washed with water (2 x 200 mL), and dried over Na_2SO_4. Removal of solvent and drying *in vacuo* provided an off-white solid (30.5 g, 26.7%, >99% ee based on chiral HPLC). Chiral HPLC method: ChiralPAK AD analytical column, 5:95 iPrOH/hexanes (both containing 0.1% TFA), 1.0 mL/min flow rate, retention times were 21.08 min and 23.40 min for the (*S,S*) and (*R,R*) isomers, respectively. ^{1}H NMR ($CDCl_3$) spectra were identical to that for the racemic (±)-*trans*-2-(4-bromo-benzoyl)-cyclopentanecarboxylic acid.

[169] *(R,R)-trans*-2-(4-Bromo-benzoyl)-cyclopentanecarboxylic acid methyl ester

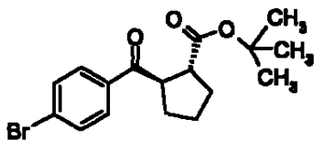


(R,R)

[170] Step 5. A suspension of (*R,R*)-*trans*-2-(4-bromo-benzoyl)-cyclopentanecarboxylic acid (30.5 g, 102.6 mmol), MeI (9.6 mL, 154.0 mmol), and $NaHCO_3$ (25.9 g, 307.9 mmol) in 360 mL DMF was stirred at rt under argon overnight. NMR analysis showed little starting material remaining. Water (1 L) was added to the reaction mixture, and then concentrated HCl was slowly added with stirring at <15°C to adjust the acidity to pH <7, and a precipitate was formed. After the mixture was stirred for 1 h, the solid was filtered and rinsed with water (200 mL). The solid was dried *in vacuo* to a constant weight, to afford the desired product as a light yellow solid (29.5 g, 92.5%, 94.5% ee based on chiral HPLC). HPLC method: ChiralPAK AD analytical column, 5:95 iPrOH/hexanes (both containing 0.1% TFA), 1.0 mL/min flow rate, retention times were 10.64 min and 12.98 min for the (*S,S*) and (*R,R*) isomers, respectively. ^{1}H NMR ($CDCl_3$) δ 7.82 (d, 2H), 7.60 (d, 2H), 4.05 (m, 1H), 3.65 (s, 3H), 3.42 (m, 1H), 2.18 (m, 2H), 1.90 (m, 1H), 1.80 (m, 3H).

[171] **Intermediate N**

(*R,R*)-2-(4-Bromo-benzoyl)-cyclopentanecarboxylic acid *tert*-butyl ester

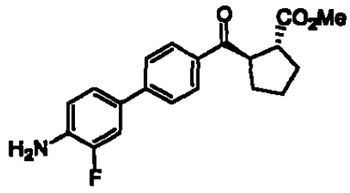


(R,R)

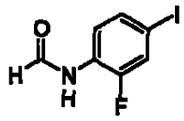
[172] (*R,R*)-*trans*-2-(4-Bromo-benzoyl)-cyclopentanecarboxylic acid (2.0 g, 6.73 mmol) was dissolved in CH_2Cl_2 (40 mL) at rt, followed by addition of a few drops of conc. sulfuric acid. Isobutylene (ca. 2.0 g) was then introduced by gentle bubbling while the reaction mixture was cooled in an ice-water bath. The reaction was then stirred at rt for 60 h and quenched by adding 40 mL saturated aqueous Na_2CO_3 solution. The organic layer was separated, washed with water, and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure afforded the desired *tert*-butyl ester as a clear oil which solidified upon standing (1.9 g, 80% yield). ^1H NMR (DMSO-d_6) δ 7.90 (d, 2H), 7.88 (d, 2H), 4.00 (q, 1H), 3.10 (q, 1H), 2.10 (m, 1H), 1.90 (m, 1H). 1.50-1.80 (m, 4H), 1.30 (s, 9H).

[173] **Intermediate O**

Methyl (1R,2R)-2-[(4'-amino-3'-fluoro-1,1'-biphenyl-4-yl)carbonyl]cyclopentanecarboxylate



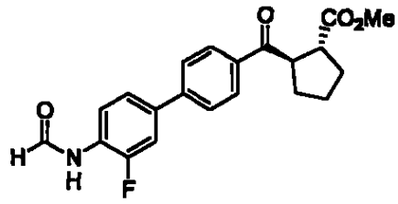
[174] **2-Fluoro-4-iodophenylformamide**



[175] **Step 1.** To a cooled solution (0°C) of 4-iodo-2 fluoroaniline (3.05 g, 12.9 mmol) in tetrahydrofuran (15 mL) and toluene (15 mL) , was slowly added a mixture of acetic anhydride (1.39 mL, 14.7 mmol) and formic acid (0.83 mL, 22.0 mmol). The reaction mixture was stirred at rt overnight, then diluted with ethyl acetate (100 mL) and 1N aqueous HCl (100 mL). The layers were separated, and the organic layer was washed with water and saturated sodium carbonate solution, and dried over sodium sulfate. The solvent was removed under reduced pressure to afford 2-fluoro-4-

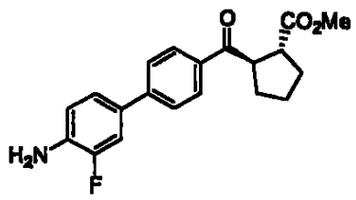
iodophenylformamide as an off-white solid (3.32 g, 97%). GC-MS ret. time 2.27 min, *m/z* 265 (M^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37-7.51 (m, 3H), 8.13 (t, 1H), 8.46 (s, 1H).

[176] Methyl (1*R*,2*R*)-2-{[3'-fluoro-4'-(formylamino)-1,1'-biphenyl-4-yl]carbonyl}cyclopentanecarboxylate



[177] Step 2. To a suspension of 2-fluoro-4-iodophenylformamide (5.11 g, 19.28 mmol) bis(pinacolato)diboron (4.89 g, 19.28 mmol), potassium acetate (5.67 g, 57.84 mmol), and palladium acetate (129 mg, 0.58 mmol) in N,N-dimethylformamide (125 mL) was bubbled through argon for 30 minutes. The reaction mixture was then heated at 80°C for 3 h. After the mixture was cooled to rt, methyl (*R,R*)-2-(4-bromobenzoyl)cyclopentanecarboxylate (2.2 g, 7.35 mmol, 97% ee), tetrakis(triphenylphosphine)palladium(0) (668 mg, 0.58 mmol), and cesium carbonate (9.43 g, 28.92 mmol) were added, and the reaction mixture was then heated at 80°C for 16 h. The mixture was then cooled to rt, quenched with water, extracted with ethyl acetate, and dried over anhydrous sodium sulfate. Solvent was then removed under reduced pressure and the crude product was purified by flash chromatography (Biotage 75) using 1:1 ethylacetate/hexane to afford methyl 2-{[3'-fluoro-4'-(formylamino)-1,1'-biphenyl-4-yl]carbonyl}cyclopentanecarboxylate (4.6 g, 65%). LC-MS ret. time 3.15 min, *m/z* 342.0 (MH^+); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52-1.94 (m, 1H), 1.92-2.07 (m, 1H), 2.10-2.21 (m, 1H), 3.48 (m, 1H), 3.55 (s, 3H), 4.12 (q, 1H), 7.59 (dd, 1H), 7.62 (dd, 1H), 7.87 (d, 2H), 8.09 (d, 2H), 8.25 (t, 1H), 8.34 (s, 1H), 10.62 (s, 1H).

[178] Methyl (1*R*,2*R*)-2-[(4'-amino-3'-fluoro-1,1'-biphenyl-4-yl)carbonyl]cyclopentanecarboxylate

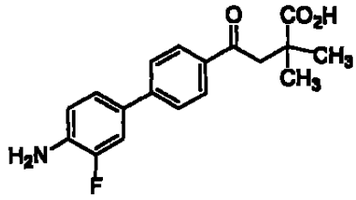


[179] Step 3. To a solution of methyl 2-{[3'-fluoro-4'-(formylamino)-1,1'-biphenyl-4-yl]-carbonyl}cyclopentanecarboxylate (4.24 g, 11.48 mmol) in methanol (34 mL) was added conc. HCl (11.4 mL), and the resulting solution was stirred at rt for 2 h. Solvent was then removed, the residual mixture was dissolved in water, and the acidity of the mixture was adjusted to pH ~7 by slow addition of saturated aqueous sodium bicarbonate solution. The mixture was then extracted

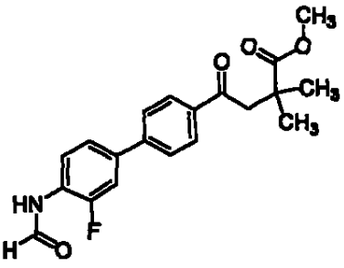
with dichloromethane and washed with saturated sodium chloride solution, dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude mixture was then triturated with ethyl acetate/hexane to afford methyl 2-[(4'-amino-3'-fluoro-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylate (3.5 g, 89%, 80% ee). *LC-MS* ret. time 3.00 min, *m/z* 370.0 (MH^+); ^1H NMR (300 MHz, DMSO-d_6) δ 1.52-1.84 (m, 4H), 1.97-2.02 (m, 1H), 2.14-2.18 (m, 1H), 3.24-3.33 (m, 1H), 3.56 (s, 3H), 4.08 (q, 1H), 5.47 (br s, 2H), 6.84 (t, 1H), 7.34 (dd, 1H), 7.48 (dd, 1H), 7.78 (d, 2H), 7.99 (d, 2H).

[180] Intermediate P

Methyl 4-(4'-amino-3'-fluoro-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate



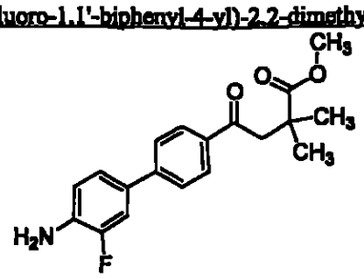
[181] Methyl 4-[3'-fluoro-4'-(formylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoate



[182] Step 1. A suspension of 2-fluoro-4-iodophenylformamide (1.94 g, 7.35 mmol, prepared as described above), bis(pinacolato)diboron (1.86 g, 7.35 mmol), potassium acetate (2.16 g, 22.1 mmol), and palladium acetate (49.4 mg, 0.22 mmol) in *N,N*-dimethylformamide (50 mL) was degassed by bubbling a flow of argon through the mixture for 30 minutes. The mixture was then heated at 80°C for 3 h. After the mixture was cooled to rt, methyl 4-(4-bromophenyl)-2,2-dimethyl-4-oxobutanoate (2.2 g, 7.4 mmol), tetrakis(triphenylphosphine)palladium(0) (254.8 mg, 0.22 mmol), and cesium carbonate (3.59 g, 11.0 mmol) were added, and the reaction mixture was heated at 80°C for 16 h. The mixture was then cooled to rt and water was added. The mixture was extracted with ethyl acetate and the combined extracts were dried over sodium sulfate. The mixture was concentrated under reduced pressure and the crude was purified by flash chromatography (Biotage Flash 40M, 1:1 ethyl acetate/hexane) to afford methyl 4-[3'-fluoro-4'-(formylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoate (1.2 g, 46%). *LC-MS* ret. time 2.80 min, *m/z* 358.1 (MH^+); ^1H NMR (300 MHz,

DMSO-d_6) δ 1.19 (s, 6H), 3.36 (s, 2H), 3.51 (s, 3H), 7.56 (d, 1H), 7.69 (dd, 1H), 7.82 (d, 2H), 7.99 (d, 3H), 8.21 (t), 10.25 (s, 1H).

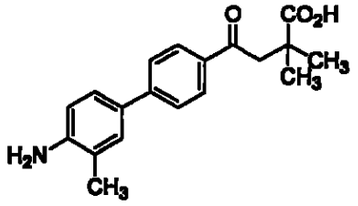
[183] Methyl 4-(4'-amino-3'-fluoro-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate



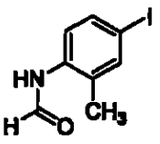
[184] Step 2. To a solution of methyl 4-[3'-fluoro-4'-(formylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoate (1.21 g, 3.39 mmol) in methanol (10 mL) was added conc. HCl (3.5 mL), and the resulting solution was stirred at rt for 16 h. The mixture was then concentrated, diluted with water, and the acidity was adjusted to pH ~7 by slow addition of saturated aqueous sodium bicarbonate solution. The mixture was then extracted with dichloromethane, and the combined organic layers were washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated under reduced pressure. The residue was then triturated with ethyl acetate/hexane to afford methyl 4-(4'-amino-3'-fluoro-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate (998 mg, 89%). LC-MS ret. time 3.11 min, *m/z* 329.9 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 6H), 3.28 (s, 2H), 3.66 (s, 3H), 6.84 (t, 1H), 7.21-7.35 (m, 2H), 7.55 (d, 2H), 7.93 (d, 2H).

[185] **Intermediate O**

Methyl 4-(4'-amino-3'-methyl-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate

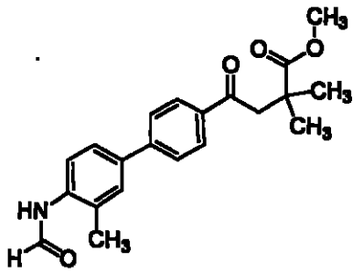


[186] 4-Iodo-2-methylphenylformamide



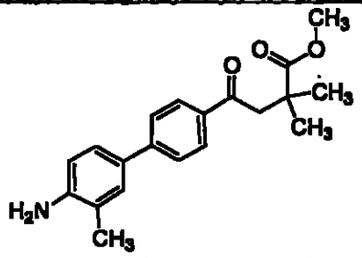
[187] Step 1. This intermediate was prepared by using a procedure similar to that described above for 2-fluoro-4-iodophenylformamide. LC-MS ret. time 2.43 min, *m/z* 262.0 (MH^+); ^1H NMR (300 MHz, DMSO-d_6) δ 2.14 (s, 3H), 7.49 (dd, 1H), 7.52-7.59 (m, 2H), 8.24 (s, 1H), 9.56 (s, 1H).

[188] Methyl 4-[4'-(formylamino)-3'-methyl-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoate



[189] Step 2. This intermediate was prepared by using a procedure similar to that described above for methyl 4-[3'-fluoro-4'-(formylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoate. LC-MS ret. time 2.78 min, *m/z* 354.1 (MH^+); ^1H NMR (300 MHz, DMSO-d_6) δ 1.02 & 1.13 (s, 6H), 2.22 & 2.28 (s, 3H), 3.36 (s, 2H), 3.51 (s, 3H), 7.29 (d) & 7.40 (s) (2H), 7.78 (d, 2H), 7.90 & 7.96 (d, 3H), 8.46 (d) (1H), 9.82 (d) (1H).

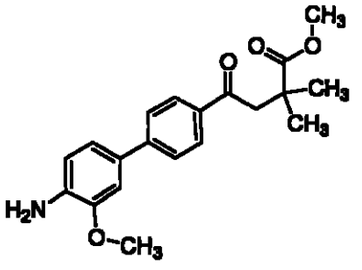
[190] Methyl 4-(4'-amino-3'-methyl-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate



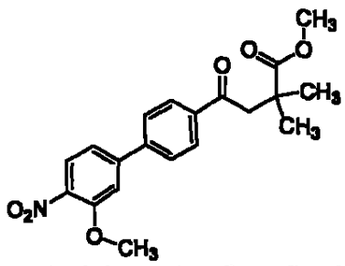
[191] Step 3. This intermediate was prepared by using a procedure similar to that described above for methyl 4-(4'-amino-3'-fluoro-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate. LC-MS ret. time 2.64 min, *m/z* 326.1 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 6H), 2.25 (s, 3H), 3.29 (s, 2H), 3.66 (s, 3H), 6.80 (s, 1H), 7.35 (s, 2H), 7.60 (d, 2H), 7.93 (d, 2H).

[192] **Intermediate R**

Methyl 4-(4'-amino-3'-methoxy-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate

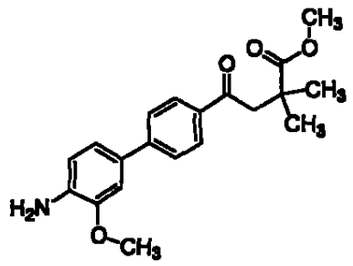


[193] Methyl 4-(3'-methoxy-4'-nitro-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate



[194] Step 1. A suspension of methyl 4-(4-bromophenyl)-2,2-dimethyl-4-oxobutanoate (200 mg, 0.67 mmol), bis(pinacolato)diboron (170 mg, 0.67 mmol), potassium acetate (197 mg, 2.01 mmol), and palladium acetate (5 mg, 0.02 mmol) in N,N-dimethylformamide (4.0 mL) was degassed by bubbling a flow of argon for 30 minutes. The reaction mixture was then heated at 80°C for 3 h. After the mixture was cooled to rt, 5-chloro-2-nitroanisole (125 mg, 0.67 mmol), tetrakis(triphenyl-phosphine)palladium(0) (23 mg, 0.02 mmol), and cesium carbonate (327 mg, 1.0 mmol) were added and the reaction mixture was heated at 80°C for 16 h. The mixture was then cooled to rt, and water was added. The aqueous layer was extracted with ethyl acetate and the combined organic phases were dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure and the residue was purified by flash chromatography (Biotage Flash 40M, 1:3 ethyl acetate/hexane) to afford methyl 4-(3'-methoxy-4'-nitro-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate (120mg, 48%). LC-MS ret. time 3.38 min, *m/z* 371.8 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 6H), 3.36 (s, 2H), 3.51 (s, 3H), 4.02 (s, 3H), 7.21-7.24 (m, 2H), 7.64-7.69 (m, 2H), 7.93 (d, 1H), 8.00-8.04 (m, 2H).

[195] Methyl 4-(4'-amino-3'-methoxy-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate

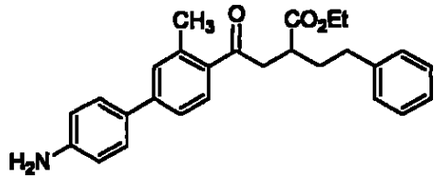


[196] Step 2. To a solution of methyl 4-(3'-methoxy-4'-nitro-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate (670 mg, 1.80 mmol) in 85% aqueous ethanol (27 mL) was added iron powder (1.01 g, 18.04 mmol) and 2 N aqueous HCl (0.9 mL, 1.8 mmol), and the resulting suspension was heated at reflux for 2.5 h. The mixture was then cooled to rt, and filtered through a pad of Celite®. Water was added, the mixture was extracted with ethyl acetate, and the combined organic phases were dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure and the residue was triturated with ethyl acetate/hexane to afford methyl 4-(4'-amino-3'-methoxy-1,1'-biphenyl-4-yl)-2,2-

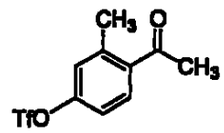
dimethyl-4-oxobutanoate (410 mg, 67%). LC-MS ret. time 2.58 min, *m/z* 342.1 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 6H), 3.28 (s, 2H), 3.66 (s, 3H), 3.90 (s, 3H), 6.75 (d, 1H), 7.02-7.09 (m, 2H), 7.59 (d, 2H), 7.94 (d, 2H).

[197] **Intermediate S**

Ethyl 4-(4'-amino-3-methyl-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenylethyl)butanoate

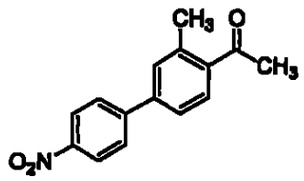


[198] 4-Acetyl-3-methylphenyl trifluoromethanesulfonate



[199] Step 1. To a cooled solution (0-5°C) of 1-(4-hydroxy-2-methylphenyl)ethanone (22.1 g, 0.147 mol) and pyridine (40.0 mL, 0.500 mol) in dichloromethane (100 mL) was slowly added trifluoromethanesulfonic anhydride (35.0 mL, 0.207 mol). After the addition was completed, the ice bath was removed, and the reaction mixture was stirred at rt for 1.5 h. Water (50 mL) was added and the layers were separated. The organic layer was washed with water (2 x 20 mL) and 0.5 N aqueous HCl, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (Biotage Flash 75, 10/90 ethyl acetate/hexane) to give 4-acetyl-3-methylphenyl trifluoromethanesulfonate as a light yellow oil (40.83 g, 90% yield). GC-MS *m/z* 282 (M^+), ret. time 8.20 min ^1H NMR ($CDCl_3$) δ 2.56 (s, 3H), 2.58 (s, 3H), 7.05-7.14 (m, 2H), 7.78 (d, 1H).

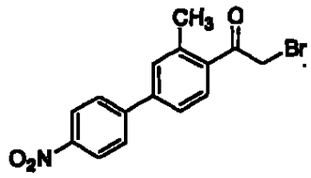
[200] 1-(3-Methyl-4'-nitro-1,1'-biphenyl-4-yl)ethanone



[201] Step 2. A mixture of 4-acetyl-3-methylphenyl trifluoromethanesulfonate (6.90 g, 24.0 mmol), 4-nitrophenylboronic acid (3.80 g, 24 mmol), 2 N aqueous sodium carbonate (88.0 mL), dioxane (88.0 mL), and toluene (296 mL) was purged with argon for 30 minutes before [1,1'-bis(diphenyl-phosphino)-ferrocene]dichloro palladium(II) (1:1 complex with dichloromethane, 1.90 g, 2.30 mmol)

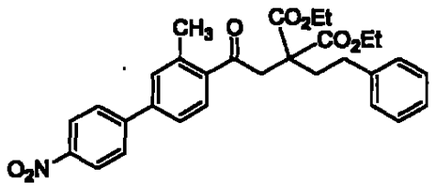
was added. The reaction mixture was heated at 85°C and stirred overnight. The layers were separated and the organic layer was washed with water (2 x 50 mL), dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. This material was purified by flash chromatography (7 to 20% ethyl acetate/hexane) to give 1-(3-methyl-4'-nitro-1,1'-biphenyl-4-yl)ethanone as a light yellow solid (6.12 g, 99% yield). GC-MS *m/z* 255 (M^+), ret. time 9.89 min; ^1H NMR ($CDCl_3$) δ: 2.61 (s, 3H), 2.62 (s, 3H), 7.49-55 (m, 2H), 7.78 (d, 2H), 7.81 (d, 1H), 8.32 (d, 2H).

[202] 2-Bromo-1-(3-methyl-4'-nitro-1,1'-biphenyl-4-yl)ethanone



[203] Step 3. A mixture of 1-(3-methyl-4'-nitro-1,1'-biphenyl-4-yl)ethanone (5.66 g, 22 mmol), pyridinium tribromide (10.63 g, 33.0 mmol), and glacial acetic acid (60 mL) was stirred at 110°C for 3 h. The reaction mixture was cooled to 0-5°C, and the precipitated product was collected by filtration and washed with small amounts of water, ethanol, and diethyl ether. The crude material was purified by flash chromatography (5:95 ethyl acetate/hexane) to give 2-bromo-1-(3-methyl-4'-nitro-1,1'-biphenyl-4-yl)ethanone as a light yellow solid (4.33 g, 59% yield). HPLC ret. time 3.63 min; ^1H NMR ($CDCl_3$) δ: 2.63 (s, 3H), 2.25 (s, 2H), 7.52-7.58 (m, 2H), 7.72-7.83 (m, 3H), 8.32 (d, 2H).

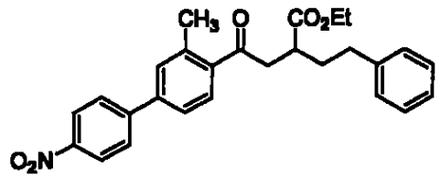
[204] Diethyl 2-[2-(3-methyl-4'-nitro-1,1'-biphenyl-4-yl)-2-oxoethyl]-2-(2-phenylethyl)malonate



[205] Step 4. To a cold suspension (0-5°C) of 95% sodium hydride (3.53 g, 13.0 mmol) in dry tetrahydrofuran (30 mL) was slowly added diethyl 2-phenylethylmalonate (3.53 g, 13 mmol). The ice bath was removed and the reaction mixture was stirred at rt for 45 minutes. A solution of 2-bromo-1-(3-methyl-4'-nitro-1,1'-biphenyl-4-yl)ethanone (4.06 g, 12.0 mmol) in dry tetrahydrofuran (50 mL) was slowly added, and the resulting mixture was stirred at rt for about 70 h. Ethyl acetate (80 mL) and water (20 mL) were added, and the layers were separated. The organic layer was washed with water (2 x 30 mL), dried over magnesium sulfate, and concentrated under reduced pressure to give a dark, brown oil. This material was purified by flash chromatography (10:90 ethyl acetate/hexane) to give diethyl 2-[2-(3-methyl-4'-nitro-1,1'-biphenyl-4-yl)-2-oxoethyl]-2-(2-phenylethyl) malonate as a light yellow oil (5.30 g, 82% yield). LC-MS ret. time 4.01 min, *m/z* 517.9 (MH^+); ^1H NMR ($CDCl_3$)

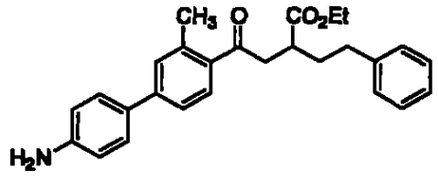
δ 1.23-1.35 (m, 6H), 2.41-2.50 (m, 2H), 2.56 (s, 3H), 2.59-2.66 (m, 2H), 3.71 (s, 2H), 4.21-4.32 (m, 4H), 7.13-7.19 (m, 3H), 7.22-7.30 (m, 2H), 7.49-7.55 (m, 2H), 7.73-7.82 (m, 3H), 8.31 (d, 2H).

[206] Ethyl 4-(3-methyl-4'-nitro-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenylethyl)butanoate.



[207] Step 5. A mixture of diethyl 2-[2-(3-methyl-4'-nitro-1,1'-biphenyl-4-yl)-2-oxoethyl]-2-(2-phenylethyl) malonate (4.87 g, 9.41 mmol), 1 N aqueous sodium hydroxide (10.4 mL, 10.40 mmol), ethanol (10 mL), and acetone (10 mL) was stirred at 50°C overnight. The mixture was concentrated and the residue was dissolved in dimethoxyethane (20 mL), and stirred at 80°C overnight. The mixture was concentrated, and the residue was dissolved in ethyl acetate (30 mL). The solution was washed with water (2 x 5 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The material obtained was purified by flash chromatography (10:90 ethyl acetate/hexane) to give ethyl 4-(3-methyl-4'-nitro-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenylethyl)butanoate as a light yellow oil (3.53 g, 99% yield). LC-MS ret. time 4.18 min, *m/z* 446.0 (MH^+); ^1H NMR ($CDCl_3$) δ: 1.33 (t, 3H), 1.83-2.17 (m, 2H), 2.58 (s, 3H), 2.67-2.78 (m, 2H), 3.00 (dd, 1H), 3.14 (m, 1H), 3.49 (dd, 1H), 4.09 (q, 2H), 7.14-7.36 (m, 5H), 7.47-7.55 (m, 2H), 7.72-7.83 (m, 3H), 8.33 (d, 2H).

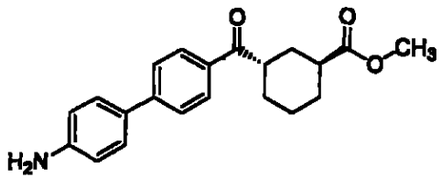
[208] Ethyl 4-(4'-amino-3-methyl-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenylethyl)butanoate



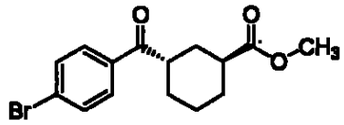
[209] Step 6. A mixture of ethyl 4-(3-methyl-4'-nitro-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenylethyl)butanoate (3.40 g, 7.60 mmol), iron powder (4.20 g, 76.00 mmol), 2 N aqueous hydrochloric acid (3.80 mL, 7.60 mmol), and 85/15 ethanol/water (100 mL) was stirred at reflux for 2.5 h. The reaction mixture was filtered through a pad of Celite®, and concentrated to give ethyl 4-(4'-amino-3-methyl-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenylethyl)butanoate as a light, brown solid (2.94 g, 93% yield). LC-MS ret. time 3.23 min, *m/z* 416.1 (MH^+); ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H), 1.82-2.17 (m, 2H), 2.58 (s, 3H), 2.68-2.77 (m, 2H), 2.98-3.09 (m, 2H), 3.49 (dd, 1H), 3.74 (br s, 2H), 4.10 (q, 2H), 6.79 (d, 2H), 7.12-7.37 (m, 5H), 7.38-7.54 (m, 4H), 7.78 (d, 1H).

[210] Intermediate T

3-(4'-Amino-biphenyl-4-carbonyl)-cyclohexanecarboxylic acid methyl ester

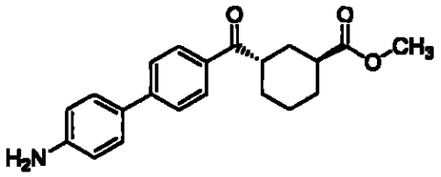


[211] 3-(4-Bromo-benzoyl)-cyclohexanecarboxylic acid methyl ester



[212] Step 1. To a solution of *trans*-3-(4-bromobenzoyl)cyclohexane-1-carboxylic acid (500 mg, 1.61 mmol, obtained from Rieke Metals Inc., Lincoln, NE, USA) and 2,2-dimethoxypropane (669 mg, 6.43 mmol) in methanol (20 mL), 5 drops of 4 M HCl in dioxane was added, and this reaction mixture was heated at 50°C overnight. The solvent was removed by rotary evaporation to give the product 3-(4-bromo-benzoyl)-cyclohexanecarboxylic acid methyl ester as a brown oil (500 mg, yield 95.7%). ^{1}H NMR (300 MHz, DMSO) δ 7.80 (d, 2 H), 7.60 (d, 2 H), 3.70 (s, 3 H), 3.25 (m, 1 H), 2.50 (m, 1 H), 2.20-1.90 (m, 4 H), 1.70-1.50 (m, 4 H); LC-MS ret. time 3.30 min, *m/z* 324.9 (MH^+).

[213] 3-(4'-Amino-biphenyl-4-carbonyl)-cyclohexanecarboxylic acid methyl ester



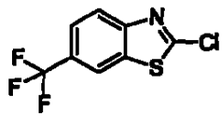
[214] Step 2. To a solution of 3-(4-bromo-benzoyl)-cyclohexanecarboxylic acid methyl ester (500 mg, 1.54 mmol) and 4-aminophenyl boronic acid (252 mg, 1.85 mmol) in toluene (40 mL) and dioxane (10 mL), 2 N aqueous Na_2CO_3 (10 mL) was added, and the mixture was degassed by bubbling with a flow of argon for 45 minutes. (1,1-Bis(diphenylphosphino)ferrocene)-dichloropalladium (63 mg, 0.08 mmol) was added to the mixture, which was then heated at 80°C overnight. The reaction mixture was cooled to rt, and then filtered through a pad of Celite®, rinsing with ethyl acetate. The organic layer was separated, washed with water and brine, and dried (Na_2SO_4). The solvent was removed by rotary evaporation, and the solid residue was purified by using a Biotage QuadUV flash chromatography system (eluant: 3:1 hexane/EtOAc). The product 3-(4'-amino-biphenyl-4-carbonyl)-cyclohexanecarboxylic acid methyl ester was obtained as a brown solid (200 mg, yield 38.5%). ^{1}H NMR (300 MHz, DMSO) δ 7.90 (d, 2 H), 7.60 (d, 2 H), 7.45 (d, 2

H), 6.80 (d, 2 H), 3.70 (s, 3 H), 3.25 (m, 1 H), 2.50 (m, 1 H), 2.20 – 1.90 (m, 4 H), 1.70-1.50 (m, 4 H); LC-MS ret. time 3.80 min (method 2), *m/z* 338.17 (MH^+).

Preparation of Compounds of Formula (VII).

[215] **Intermediate U**

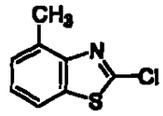
2-Chloro-6-(trifluoromethyl)-1,3-benzothiazole



[216] In a three-necked flask fitted with a condenser, a suspension of copper II chloride (370 mg, 2.75 mmol) in acetonitrile (5 mL) was treated with *tert*-butyl nitrite (0.41 mL, 3.44 mmol) and stirred at rt for 10 minutes. A solution of 2-amino-6-trifluoromethylbenzthiazole (500 mg, 2.29 mmol) in acetonitrile (1 mL) was then added dropwise. The mixture was heated at 65°C for 30 minutes, then cooled and diluted with an excess of 1 N aqueous hydrochloric acid solution. The mixture was extracted with ethyl acetate. The organic phase was separated, dried ($MgSO_4$), and concentrated under reduced pressure. An orange semi-solid (501 mg, 92%) was obtained and used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 8.10-8.05 (m, 2 H), 7.74 (d, 1 H); LC-MS *m/z* 238.2 (MH^+), ret. time 3.76 min TLC R_f= 0.50 (9:1 hexanes / ethyl acetate).

[217] **Intermediate V**

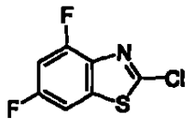
2-Chloro-4-methyl-1, 3-benzothiazole



[218] To a solution containing copper chloride (II) (1.96 g, 14.61 mmol) and tri(ethylene glycol) dimethyl ether (6 mL) in acetonitrile (100 mL) was added isoamyl nitrite (2.14 g, 18.27 mmol), and the reaction mixture was stirred at rt for 30 minutes. To this suspension was added dropwise a solution of 2-amino-4-methylbenzothiazole (2.0 g, 12.18 mmol) in tri(ethylene glycol) dimethyl ether (10 mL). The reaction mixture was stirred at rt for 10 minutes, and then heated at 50°C for 2.5 h. The reaction mixture was cooled to rt, and then poured cautiously into cold aqueous 6 M HCl (400 mL). The solution was extracted with EtOAc. The organic layer was washed with HCl (1.0 M), water, brine, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Biotage Flash 40M) using 5% ethyl acetate in hexane to afford 2-chloro-4-methyl-1, 3-benzothiazole (1.6 g, 71%). ^1H NMR (400 MHz, CD_2Cl_2) δ 2.70 (s, 3H), 7.32 (m, 2H), 7.64 (m, 1H).

[219] **Intermediate W**

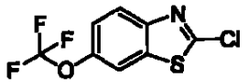
2-Chloro-4, 6-difluoro-1,3-benzothiazole



[220] To a solution containing copper chloride (II) (0.87 g, 6.45 mmol) and tri(ethylene glycol) dimethyl ether (3 mL) in acetonitrile (50 mL) was added isoamyl nitrite (0.94 g, 8.06 mmol), and the reaction mixture was stirred at rt for 30 minutes. To this suspension was added dropwise a solution of 4,6-difluoro-1,3-benzothiazol-2-amine (1.0 g, 5.37 mmol) in tri(ethylene glycol) dimethyl ether (5 mL). The reaction mixture was stirred at rt for 10 minutes, and then heated at 50°C for 2.5 h. The reaction mixture was cooled to rt, and then poured cautiously into cold aqueous 6 M HCl (200 mL). The solution was extracted with EtOAc. The organic layer was washed with HCl (1.0 M), water and brine, filtered and concentrated down to afford 2-chloro-4,6-difluoro-1,3-benzothiazole (1.1 g, 99%). ^{1}H NMR (400 MHz, DMSO-d_6) 7.05 (m, 1H), 7.36 (m, 1H).

[221] **Intermediate X**

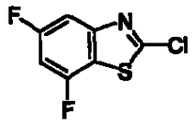
2-Chloro-6-trifluoromethoxy-1,3-benzothiazole



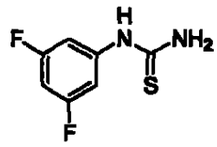
[222] To a solution containing dry copper (II) chloride (3.44 g, 25.62 mmol) and tri(ethylene glycol) dimethyl ether (10 g) in acetonitrile (150 mL) was added isoamyl nitrite (4.5 mL, 32.02 mmol). The reaction mixture was stirred at rt under argon for 30 minutes. To this suspension was added dropwise, a solution containing 6-trifluoromethoxy-1,3-benzothiazol-2-ylamine (5 g, 21.35 mmol) and tri(ethylene glycol) dimethyl ether (10 g). The reaction mixture was stirred at rt for 10 minutes, and then heated at 50°C for 3 h. The mixture was cooled to rt, poured cautiously into aqueous 6 N HCl, and extracted with ethyl acetate. The organic layer was washed with 1N aqueous HCl and brine, and concentrated under reduced pressure to give the desired compound in near-quantitative yield, which was used without further purification in the next step.

[223] Intermediate Y

2-Chloro-5,7-difluoro-1,3-benzothiazole

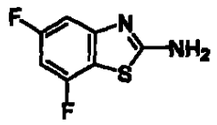


[224] N-(3,5-Difluorophenyl) thiourea



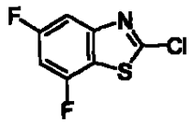
[225] Step 1. Benzoyl chloride (5.44 g, 38.73 mmol) was added to a stirred solution of ammonium thiocyanate (3.83 g, 50.35 mmol) in acetone (80 mL) at 30°C. The mixture was stirred at reflux for 30 minutes, then cooled to 50°C, and a solution of 3,5-difluoroaniline (5.00 g, 38.73 mmol) in acetone (10 mL) was added in one portion. The mixture was stirred at reflux for 30 minutes. A solution of NaOH (5.42 g, 135.54 mmol) in water (65 mL) was added, and the mixture was stirred at reflux for 20 minutes and then cooled to 20°C. Concentrated HCl was added to adjust the acidity to pH = 5, and then the mixture was adjusted to slightly alkaline by the addition of conc. ammonium hydroxide. After 30 minutes, the mixture was cooled to 10°C and extracted with EtOAc, and the combined organic layer was washed with brine, filtered, and concentrated to afford N-(3,5-difluorophenyl) thiourea (3.52 g, 48%). ret. time 1.73; *m/z* 189.0 (MH^+); ^1H NMR (400 MHz, MeOH-d_4) δ 6.72 (m, 1H), 7.16 (m, 2H).

[226] 5,7-Difluoro-1,3-benzothiazol-2-amine



[227] Step 2. To a suspension of N-(3,5-difluorophenyl) thiourea (3.40 g, 18.07 mmol) in DCE (95 mL) was added a solution of bromine in DCE (5 mL) below 30°C. The mixture was heated at reflux for 2.5 h, then cooled to 10°C, and the precipitate formed was collected by filtration and washed with DCE. The solid was stirred with water (200 mL), basified by treatment with conc. ammonium hydroxide, filtered, and dried in a vacuum oven to afford 5,7-difluoro-1,3-benzothiazol-2-amine (3.05 g, 90%). ret. time 2.18; *m/z* 187.1 (MH^+); ^1H NMR (400 MHz, DMSO-d_6) δ 6.92 (m, 1H), 7.00 (m, 2H), 7.92 (s, 2H).

[228] 2-Chloro-5,7-difluoro-1,3-benzothiazole



[229] Step 3. To a solution containing copper chloride (II) (0.89 g, 6.64 mmol) and tri(ethylene glycol) dimethyl ether (6 mL) in acetonitrile (60 mL) was added isoamyl nitrite (0.97 g, 8.30 mmol) and the reaction mixture was stirred at rt for 30 minutes. To this suspension was added dropwise a solution of 5,7-difluoro-1,3-benzothiazol-2-amine (1.03 g, 5.53 mmol) in tri(ethylene glycol) dimethyl ether (20 mL) and acetonitrile (30 mL). The reaction mixture was stirred at rt for 10 minutes and heated at 50°C for 2.5 h. The reaction mixture was cooled to rt, and then poured cautiously into cold aqueous 6 M HCl (400 mL). The solution was extracted with EtOAc. The organic layer was washed with HCl (1.0 M), water and brine, filtered, and concentrated. The residue was purified by flash chromatography (Biotage Flash 40M) using 5% ethyl acetate in hexane to afford 2-chloro-5,7-difluoro-1,3-benzothiazole (0.55 g, 48%). ^{1}H NMR (400 MHz, CD_2Cl_2) 7.02 (m, 1H), 7.52 (m, 1H).

[230] In a similar manner to the procedures described above, additional 2-chloro-1,3-benzothiazoles were prepared from the corresponding 2-amino-1,3-benzothiazoles, such as:

(a) 2-chloro-6-ethoxy-1,3-benzothiazole (LC-MS *m/z* 214.2 (MH^+), ret. time 3.09 min);

(b) 2-chloro-6-fluoro-1,3-benzothiazole (HPLC ret. time 2.85 min);

(c) 2-chloro-6-methyl-1,3-benzothiazole (LC-MS *m/z* 184.2 (MH^+), ret. time 3.09 min);

(d) 2-chloro-5,7-dimethyl-1,3-benzothiazole (LC-MS *m/z* 198.1 (MH^+), ret. time 3.36 min);

(e) 2-chloro-5,6-dimethyl-1,3-benzothiazole (LC-MS *m/z* 198.2 (MH^+), ret. time 3.34 min);

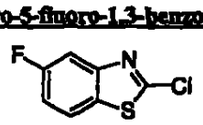
(f) 2-chloro-6-methylsulfonyl-1,3-benzothiazole (HPLC ret. time 2.18 min); and

(g) 2-chloro-5,7-difluoro-1,3-benzothiazole (TLC Rf 0.65, 40% EtOAc in hexane).

[231] In certain cases the requisite 2-amino-1,3-benzothiazole was prepared from the corresponding thiourea as described above for the preparation of N-(3,5-difluorophenyl) thiourea and 5,7-difluoro-1,3-benzothiazol-2-amine.

[232] Intermediate Z

2-Chloro-5-fluoro-1,3-benzothiazole

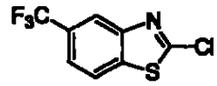


[233] Sulfuryl chloride (50 μL, 0.65 mmol) was added neat to 5-fluoro-1,3-benzothiazole-2-thiol (100 mg, 0.54 mmol). The mixture was stirred at ambient temperature for 1 h, then heated at 60°C for 30 minutes. The resulting solution was cooled to rt, and poured onto ice. The title compound was

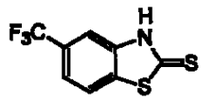
collected by filtration, washed with water, and dried under vacuum. The solid obtained was used without further purification; LC-MS *m/z* 188.1 (MH^+), ret. time 3.27 min.

[234] **Intermediate AA**

2-Chloro-5-(trifluoromethyl)benzothiazole

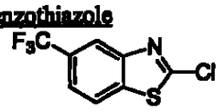


[235] 2-Mercapto-5-(trifluoromethyl)benzothiazole



[236] Step 1. To a mixture of sodium hydride (0.98g, 40.91 mmol) and diethylene glycol monoethyl ether (25 mL) was added 2-chloro-5-(trifluoromethyl)aniline (5.00 g, 25.57 mmol) under a nitrogen atmosphere. The resulting mixture was stirred at rt for 30 minutes, and then carbon disulfide (3.89 g, 51.13 mmol) was added. The reaction mixture was then heated at 140°C for 6 hours. After cooling the solution to rt, the product was precipitated by addition of conc. HCl, collected by filtration, and recrystallized from isopropyl ether to afford 2-mercapto-5-(trifluoromethyl)benzothiazole (2.65 g, 44%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.49 (s, 1H), 7.61 (d, 1H), 7.94 (d, 1H).

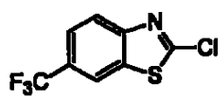
[237] 2-Chloro-5-(trifluoromethyl)benzothiazole



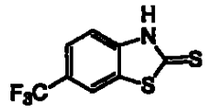
[238] Step 2. Sulfuryl chloride (9.09 g, 67.33 mmol) was added with stirring to 2-mercapto-5-(trifluoromethyl)benzothiazole (2.64 g, 11.22 mmol) over a period of 5 minutes. The reaction mixture was then allowed to stand for approximately 1 h. Ice water was added to the reaction mixture with stirring to decompose the excess of sulfuryl chloride, and the product was then extracted with ethyl acetate. The organic layer was washed with water (3x) and brine, dried over anhydrous Na_2SO_4 and concentrated. The resulting solid was dissolved in EtOAc and filtered though a short silica-gel column, eluting with EtOAc, to give 2-chloro-5-(trifluoromethyl)benzothiazole (2.50 g, 94%). LC-MS *m/z* 238.0 (MH^+), ret. time 2.55 min; ^1H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, 1H), 8.38 (m, 2H).

[239] **Intermediate BB**

2-Chloro-6-(trifluoromethyl)benzothiazole

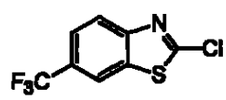


[240] 2-Mercapto-6-(trifluoromethyl)benzothiazole



[241] Step 1. A mixture of 2-chloro-4-trifluoromethylaniline (15.0 g, 76.7 mmol) and potassium *O*-ethyl dithiocarbonate (29.5 g, 184.1 mmol) in 75 mL anhydrous DMF was heated at 130°C overnight under a nitrogen atmosphere. The reaction mixture was cooled to rt, and then 1 N HCl solution (200 mL) was added with stirring to induce precipitation. After the mixture was stirred for 30 minutes, the solid precipitate was collected by filtration and rinsed with water. The filter cake was dissolved in 100 mL EtOAc, and the solution was dried over Na_2SO_4. EtOAc was removed by rotary evaporation, and the residue was dried *in vacuo* to afford the desired product as a white solid (18.0 g, 99%). ^{1}H NMR (DMSO-d_6) δ 14.00 (bs, 1 H), 8.20 (s, 1 H), 7.70 (d, 1 H), 7.40 (d, 1 H); GC- EIMS *m/z* 235 (M^+).

[242] 2-Chloro-6-(trifluoromethyl)benzothiazole

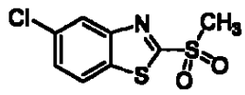


[243] Step 2. Sulfuryl chloride (40 mL) was added with stirring to 2-mercapto-6-(trifluoromethyl)-benzothiazole (18.0 g, 76.7 mmol) at <20°C under a nitrogen atmosphere, and the suspension was then stirred at rt for 2 h. The reaction mixture was poured into ice water with stirring. Precipitation was formed, and stirring was continued for 2 h. The solid precipitate was filtered, and rinsed with water. The wet filter cake was dissolved in 100 mL EtOAc, and the solution was washed with 100 mL water and 50 mL saturated aqueous $NaHCO_3$ solution, then dried over Na_2SO_4. EtOAc was removed by rotary evaporation, and the residue was dried *in vacuo* to afford the desired product as a light yellow solid (16.5 g, 91%). GC-EIMS *m/z* 237 (M^+); ^{1}H NMR ($CDCl_3$) δ 8.10 (s, 1 H), 8.00 (d, 1 H), 7.70 (d, 1 H).

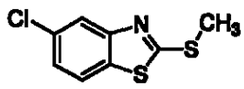
[244] In a similar manner to the procedures described above, additional 2-chloro-1,3-benzothiazoles were prepared from the corresponding 2-mercapto-1,3-benzothiazoles, such as 2-chloro-5-fluoro-1,3-benzothiazole (LC-MS *m/z* 188.1 (MH^+), ret. time 3.27 min). Additional 2-chloro-1,3-benzothiazoles were commercially available, such as 2-chloro-benzothiazole, 2,6-dichlorobenzothiazole, 2,4-dichlorobenzothiazole, 2-chloro-6-methoxy-1,3-benzothiazole, 2-chloro-5-methoxy-1,3-benzothiazole, and 2-chloro-6-nitro-1,3-benzothiazole. Certain 2-bromo-thiazoles were commercially available, such as 2-bromo-thiazole and 2-bromo-5-nitro-thiazole.

[245] Intermediate CC

5-Chloro-2-methanesulfonylbenzothiazole

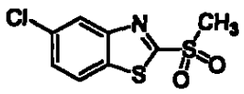


[246] 5-Chloro-2-methylsulfanyl-benzothiazole



[247] Step 1. To 5-chlorobenzothiazole-2-thiol (1.00 g, 4.96 mmol) in anhydrous tetrahydrofuran (20 mL) was added powdered potassium carbonate (1.37 g, 9.92 mmol) as a solid. Iodomethane (0.62 mL, 1.41 g, 9.92 mmol) was then added neat to the mixture, with rapid stirring. After stirring for 18 h, solids were removed by filtration. The filtrate was concentrated under vacuum to provide the title compound as a waxy yellow solid (1.0 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1 H), 7.57 (d, 1 H), 7.21-7.17 (m, 1 H), 2.72 (s, 3 H); LC-MS *m/z* 216.2 (MH^+), retention time 3.20 minutes. TLC R_f 0.72 (2:1 hexanes / ethyl acetate).

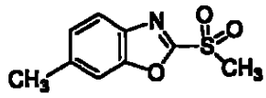
[248] 5-Chloro-2-methanesulfonylbenzothiazole



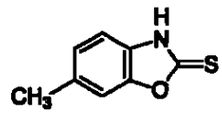
[249] Step 2. To a 0°C solution of 5-chloro-2-methylsulfanyl-benzothiazole (1.00 g, 4.64 mmol) in dichloromethane (25 mL) was added 3-chloroperoxybenzoic acid (50%, 3.20 g, 9.27 mmol). The solution was stirred at rt for 24 h, and saturated aqueous $Na_2S_2O_3$ solution was added to destroy any unreacted peracid. The layers were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, then dried ($MgSO_4$) and concentrated under reduced pressure to a yellow solid. The crude solid was triturated with hexanes, collected by filtration, and air-dried to provide the title compound as a pale yellow solid (0.96 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1 H), 8.04 (d, 1 H), 7.41 (dd, 1 H), 3.40 (s, 3 H); LC-MS *m/z* 248.0 (MH^+), retention time 3.05 minutes. TLC R_f 0.36 (2:1 hexanes / ethyl acetate).

[250] Intermediate DD

6-Methyl-2-(methylsulfonyl)-1,3-benzoxazole

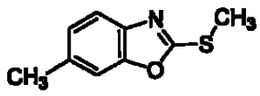


[251] 6-Methyl-1,3-benzoxazole-2(3H)-thione



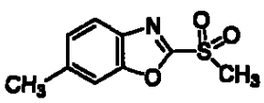
[252] Step 1. A mixture of 6-amino-m-cresol (593.7 mg, 4.82 mmol) and potassium O-ethyl xanthate (850 mg, 5.30 mmol) in pyridine (10 mL) was stirred and heated to reflux for 2 h. It was cooled to rt, poured into a mixture of ice-water (40 mL), and concentrated HCl (4 mL). The solid was collected, washed with water, and dried in the hood overnight and then in a vacuum oven at 45°C for 3 h. The product 6-methyl-1,3-benzoxazole-2(3H)-thione was obtained as beige powder (735 mg, yield 92.3%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.10 (s, 1 H), 7.03 (d, 2 H), 2.42 (s, 3H); LC-MS ret. time 2.37 min (method 2), *m/z* 166.0 (MH^+).

[253] 6-Methyl-2-(methylsulfanyl)-1,3-benzoxazole



[254] Step 2. 6-Methyl-1,3-benzoxazole-2(3H)-thione (375 mg, 2.27 mmol) was dissolved in THF (2.0 mL), and iodomethane (1610.8 mg, 11.35 mmol) and potassium carbonate (627.36 mg, 4.54 mmol) were added. This reaction mixture was stirred vigorously at rt overnight. The reaction mixture was filtered and the solid was rinsed with additional THF. The filtrate was concentrated *in vacuo* to a yellow solid. The solid was partitioned between ethyl acetate and water. The organic layer was separated and washed with brine, dried with $MgSO_4$, and concentrated. The solid was dried for 1 h in a 50°C oven. The product 6-methyl-2-(methylsulfanyl)-1,3-benzoxazole was obtained as yellow solid (145 mg, 35.6%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50 (d, 1 H), 7.20 (s, 1 H), 7.10 (d, 1 H), 2.78 (s, 3 H), 2.42 (s, 3 H); LC-MS ret. time 2.90 min (method 2), *m/z* 180.1 (MH^+).

[255] 6-Methyl-2-(methylsulfonyl)-1,3-benzoxazole



[256] Step 3. *meta*-Chloroperoxybenzoic acid (1.37 g, 6.14 mmol) was added to a solution of 6-methyl-2-(methylsulfanyl)-1,3-benzoxazole (500 mg, 2.79 mmol) in dichloromethane (20 mL) at 0°C.

The reaction was warmed to rt and stirred at rt for a total of 48 h. The reaction was transferred to a separatory funnel, washed with saturated aqueous $NaHCO_3$ (3 x 5 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated without heating. The product 6-methyl-2-(methylsulfonyl)-1,3-benzoxazole (200 mg, 33.9%) was obtained as pale yellow solid. GC-MS ret. time 10.53 min, *m/z* 211 (MH^+).

[257] In a similar manner to the preceding example, the following 2-(methylsulfonyl)-1,3-benzoxazoles were prepared:

(a) 6-chloro-2-(methylsulfonyl)-1,3-benzoxazole;

(b) 6-methoxy-2-(methylsulfonyl)-1,3-benzoxazole;

(c) 5-methyl-2-(methylsulfonyl)-1,3-benzoxazole;

(d) 4-methyl-2-(methylsulfonyl)-1,3-benzoxazole;

(e) 2-(methylsulfonyl)-5,6,7,8-tetrahydronaphtho[2,3-d][1,3]oxazole;

(f) 5-fluoro-2-(methylsulfonyl)-1,3-benzoxazole;

(g) 6-fluoro-2-(methylsulfonyl)-1,3-benzoxazole;

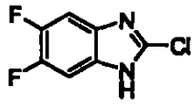
(h) 5-isopropyl-2-(methylsulfonyl)-1,3-benzoxazole;

(i) 5-*n*-propyl-2-(methylsulfonyl)-1,3-benzoxazole; and

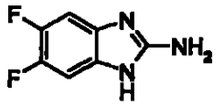
(j) 5,6-dimethyl-2-(methylsulfonyl)-1,3-benzoxazole.

[258] **Intermediate EE**

2-Chloro-5,6-difluoro-1H-benzimidazole

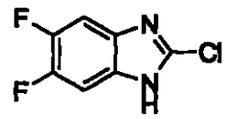


[259] 5,6-Difluoro-1H-benzimidazol-2-amine



[260] Step 1. The procedure used was similar to that reported in J. Med. Chem. 40:811-818, 1997. A solution of 1,2-diamino-4,5-difluorobenzene (500 mg, 3.47 mmol) in water (5 mL) was cooled to 0°C and then treated with a solution of cyanogen bromide (0.83 mL, 4.16 mmol, 5 M in acetonitrile) and solid sodium bicarbonate (583 mg, 6.94 mmol). The solution was stirred at rt overnight and was then concentrated *in vacuo*. The dark residue was suspended in ethanol and heated at reflux for 15 minutes. The hot suspension was filtered, rinsing with hot ethanol, and the filtrate was concentrated *in vacuo* to afford 5,6-difluoro-1H-benzimidazol-2-amine (580 mg, 59%), which was used in the next step without further purification. LC-MS *m/z* 170.2 (MH^+), ret. time 0.85 min; ^1H NMR (300 MHz, DMSO-d_6) δ 6.30 (br s, 2H), 7.06 (dd, 2H), 10.79 (br s, 1H).

[261] 2-Chloro-5,6-difluoro-1H-benzimidazole



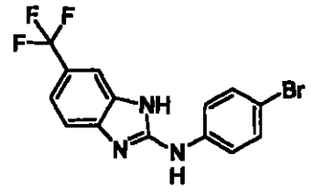
[262] Step 2. The procedure used was similar to that reported in J. Med. Chem. 40:811-818, 1997. To a mixture of copper(II) chloride (795 mg, 5.91 mmol) in acetone (20 mL) was added tert-butyl nitrite (0.53 mL, 4.43 mmol). The reaction mixture was stirred at rt for 20 minutes, 5,6-difluoro-1H-benzimidazol-2-amine (500 mg, 2.96 mmol) was then added, and the mixture was heated at reflux for 2 h (with additional portions of tert-butyl nitrite added every 0.5 h). The reaction mixture was then cooled to rt, treated with 2 N HCl, and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated *in vacuo* to afford 2-chloro-5,6-difluoro-1H-benzimidazole (580 mg, 73%), which was used without further purification in the next step. LC-MS *m/z* 189.2 (MH^+), ret. time 1.96 min; ^1H NMR (300 MHz, DMSO-d_6) δ 7.62 (t, 2H), 13.5 (br s, 1H).

[263] Certain 2-chlorobenzimidazoles were commercially available such as 2-chlorobenzimidazole and 2-chloro-5-methoxybenzimidazole.

Preparation of Compounds of Formula (IX)

[264] Intermediate FF

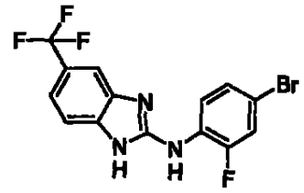
N-(4-Bromophenyl)-6-(trifluoromethyl)-1H-benzimidazol-2-amine



[265] 1,2-Diamino-5-trifluoromethylbenzene (0.25 g, 1.42 mmol) was diluted in toluene (5 mL) and treated with 4-bromophenylisothiocyanate (0.30 g, 1.42 mmol). The dark solution was stirred at 100°C for 15 minutes, then treated with 1,3-dicyclohexylcarbodiimide (0.44 g, 2.13 mmol). The reaction was maintained at 100°C for 5 h. The reaction was concentrated and partitioned between ethyl acetate and water. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The dark brown oil was purified by flash chromatography on silica gel, eluting with a gradient from 9:1 hexanes / ethyl acetate to 100% ethyl acetate. The title compound was obtained as a light pink solid (0.50 g, 30%). ^1H NMR (300 MHz, DMSO-d_6) δ 11.3 (broad d, 1 H), 9.87 (d, 1 H), 7.50 (d, 2 H), 7.61 (d, 1 H), 7.55-7.42 (m, 3 H), 7.35-7.30 (m, 1 H); LC/MS *m/z* 356.2 (MH^+), retention time 2.33 minutes.

[266] Intermediate GG

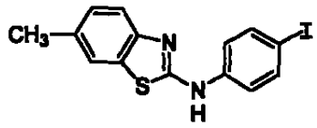
N-(4-Bromo-2-fluorophenyl)-N-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]amine



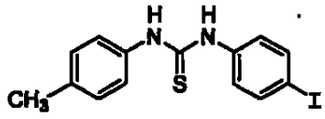
[267] 1,2-Diamino-5-trifluoromethylbenzene (0.50 g, 2.84 mmol) was diluted in dichloromethane (5 mL) and treated with 4-bromo-2-fluoro-phenylisothiocyanate (0.66 g, 2.84 mmol). The dark solution was stirred at 45°C for 15 minutes, then 1,3-dicyclohexylcarbodiimide (0.44 g, 2.13 mmol) was added all at once. The reaction was heated in a 45°C oil bath overnight, then cooled and concentrated at reduced pressure. The dark residue was diluted with ethyl acetate, and the organic layer was washed with water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The resulting dark brown oil was purified by flash chromatography on silica gel eluted on a gradient from 9:1 hexanes / ethyl acetate to 100% ethyl acetate. The title compound was collected as a light pink solid (0.60 g, 57%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.3 (broad d, 1H), 9.87 (d, 1H), 7.50 (d, 2H), 7.61 (d, 1H), 7.55-7.41 (m, 3H), 7.35-7.30 (m, 1H); LC/MS *m/z* 356.2 (MH^+), retention time 2.33 minutes.

[268] Intermediate HH

N-(4-Iodophenyl)-6-methyl-1,3-benzothiazol-2-amine

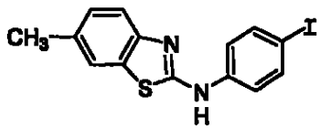


[269] N-(4-Iodophenyl)-N'-(4-methylphenyl) thiourea



[270] Step 1. A solution of *p*-tolyl thiocyanate (0.65 g, 4.35 mmol) and *p*-iodo-aniline (1.00 g, 4.57 mmol) in EtOH was heated at reflux for 3 h. Then the reaction mixture was diluted with EtOH and the precipitate was collected by filtration, washed with EtOH and ether, and dried in a vacuum oven to give N-(4-iodophenyl)-N'-(4-methylphenyl) thiourea (1.32 g, 90% purity, 74% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.78 (s, 3H), 7.12 (d, 2H), 7.29 (m, 4H), 7.63 (m, 2H), 9.72 (s, 1H), 9.76 (s, 1H).

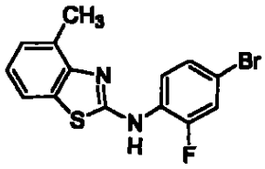
[271] N-(4-Iodophenyl)-6-methyl-1,3-benzothiazol-2-amine



[272] Step 2. A suspension of N-(4-iodophenyl)-N'-(4-methylphenyl) thiourea (0.62 g, 4.68 mmol) in chloroform (23 mL) was treated with a solution of bromine (2.65 g, 16.59 mmol) in chloroform (1 mL). The reaction mixture was stirred at rt for 5 minutes and then heated at 50°C for 5 minutes. Then the reaction mixture was allowed to cool, and was treated with sulphurous acid until the orange color disappeared. The reaction mixture was neutralized by treatment with conc. ammonium hydroxide. More chloroform was then added to dissolve the precipitate. The layers was separated, and the organic layer was washed with water and brine, dried over sodium sulfate, filtered and concentrated to give N-(4-iodophenyl)-6-methyl-1,3-benzothiazol-2-amine (0.6 g, 97%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.36 (s, 3H), 7.12 (m, 1H), 7.48 (d, 1H), 7.60 (m, 3H), 7.65 (m, 2H), 10.50 (s, 1H).

[273] Intermediate II

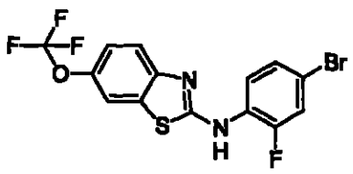
N-(4-Bromo-2-fluorophenyl)-4-methyl-1,3-benzothiazol-2-amine



[274] To a solution of 2-chloro-4-methyl-1,3-benzothiazole (0.25 g, 1.36 mmol) in n-BuOH (8 mL) was added 4-bromo-2-fluoroaniline (0.52 g, 2.72 mmol) and HCl (4.0 M in dioxane, 0.5 mL). The reaction was heated at 90°C overnight. Solvent was removed by rotary evaporation and 1 N aqueous HCl was added. The aqueous layer was separated and extracted with EtOAc. The combined organic phases were washed with 1 N aqueous HCl and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was brought up in MeOH and the precipitate was collected by filtration, washed with MeOH, and dried in a vacuum oven to give N-(4-bromo-2-fluorophenyl)-4-methyl-1,3-benzothiazol-2-amine (0.41 g, 89%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.62 (s, 3H), 7.07 (t, 1H), 7.15 (d, 1H), 7.36 (m, 2H), 7.51 (d, 1H), 8.72 (t, 1H).

[275] **Intermediate JJ**

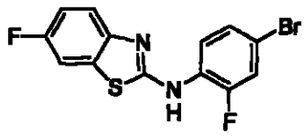
***N*-(4-Bromo-2-fluorophenyl)-*N*-(6-trifluoromethoxy-1,3-benzothiazol-2-yl)amine**



[276] In a 250-mL round-bottom flask, 2-chloro-6-trifluoromethoxy-1,3-benzothiazole (5.36 g, 21.14 mmol) and 4-bromo-2-fluoroaniline (4.82 g, 25.36 mmol) were combined in 100 mL n-butanol containing 1% 4.0 M HCl in dioxane, and heated at 90°C overnight. The mixture was cooled to rt and the solvent was removed under reduced pressure. Ethyl acetate (50 mL) was added, and the mixture was ultrasonicated by suspending the flask in an ultrasonication bath for 30 minutes. The mixture was filtered, and the filtrate was concentrated under reduced pressure. Acetonitrile (50 mL) was added to the mixture, which was then ultrasonicated for 30 minutes and then filtered to provide the product as a white solid (5 g, 58%). LC-MS *m/z* 409.1 (MH^+), ret. time 4.02 min.

[277] **Intermediate KK**

***N*-(4-Bromo-2-fluorophenyl)-*N*-(6-fluoro-1,3-benzothiazol-2-yl)amine**



[278] In a similar manner to that described above for the preparation of *N*-(4-bromo-2-fluorophenyl)-4-methyl-1,3-benzothiazol-2-amine and *N*-(4-bromo-2-fluorophenyl)-*N*-(6-trifluoromethoxy-1,3-benzothiazol-2-yl)amine, using 2-chloro-6-fluoro-1,3-benzothiazole and 2-fluoro-4-bromoaniline, was prepared the desired product as a white solid (78% yield). ^1H NMR (400 MHz, 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).

[279] In a similar manner to the procedures described above, the following *N*-(4-bromophenyl)-*N*-(1,3-benzothiazol-2-yl)amines were prepared from the appropriate 4-bromoanilines and 2-chloro-1,3-benzothiazoles:

(a) *N*-(4-bromophenyl)-*N*-(5-trifluoromethyl-1,3-benzothiazol-2-yl)amine (LC-MS *m/z* 373.0 (MH^+), ret. time 3.92 min);

(b) *N*-(4-bromo-2-fluorophenyl)-*N*-(5-trifluoromethyl-1,3-benzothiazol-2-yl)amine (LC-MS *m/z* 391.0 (MH^+), ret. time 4.04 min (method 2));

(c) *N*-(4-bromo-2-fluorophenyl)-*N*-(6-trifluoromethyl-1,3-benzothiazol-2-yl)amine (LC-MS *m/z* 391.0 (MH^+), ret. time 3.95 min);

(d) *N*-(4-bromo-2-fluorophenyl)-*N*-(5,7-dimethyl-1,3-benzothiazol-2-yl)amine

(LC-MS *m/z* 353.1 (MH^+), ret. time 4.09 min);

(e) *N*-(4-bromo-2-fluorophenyl)-*N*-(5,7-difluoro-1,3-benzothiazol-2-yl)amine (LC-MS *m/z* 359.1 (MH^+), ret. time 3.86 min);

(f) *N*-(4-bromo-2-fluorophenyl)-*N*-(6-methoxy-1,3-benzothiazol-2-yl)amine (LC-MS *m/z* 353.2 (MH^+), ret. time 3.55 min);

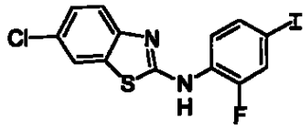
(g) *N*-(4-bromo-2-fluorophenyl)-*N*-(1,3-benzothiazol-2-yl)amine (LC-MS *m/z* 323.1 (MH^+), ret. time 3.55 min);

(h) *N*-(4-bromophenyl)-*N*-(6-isopropyl-1,3-benzothiazol-2-yl)amine (LC-MS *m/z* 347.2 (MH^+), ret. time 4.44 min); and

(i) *N*-(4-bromo-2-fluorophenyl)-*N*-(6-isopropyl-1,3-benzothiazol-2-yl)amine (LC-MS *m/z* 365.2 (MH^+), ret. time 4.57 min).

[280] **Intermediate LL**

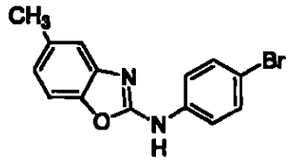
N-(4-Iodo-2-fluorophenyl)-6-chloro-1,3-benzothiazol-2-amine



[281] A mixture of 2,6-dichlorobenzothiazole (1.0 g, 4.9 mmol) and 2-fluoro-4-iodoaniline (2.32 g, 9.8 mmol) in 20 mL BuOH was stirred at 90°C, and then HCl (4 M in dioxane, 1.0 mL) was added. The reaction mixture was stirred with heating at 90°C overnight, under argon. NMR analysis then showed little 2,6-dichlorobenzothiazole remaining. After BuOH was removed by rotary evaporation, EtOAc (100 mL) and 1 N aqueous HCl (100 mL) were added. The organic layer was separated and washed with 1 N aqueous HCl (100 mL), saturated $Na_2O_2S_3$ solution (50 mL), water (100 mL), and then dried over Na_2SO_4. Removal of solvent under reduced pressure afforded a residue, which was triturated with EtOAc (10 mL) and hexanes (40 mL). The solid was filtered and dried *in vacuo* to a constant weight, to afford the desired product as a light purple solid (0.75 g, 38%). ^1H NMR (DMSO-d_6) δ 10.45 (s, 1H), 8.35 (t, 1H), 7.95 (s, 1H), 7.70 (d, 1H), 7.58 (d, 2H), 7.30 (d, 1H).

[282] Intermediate MM

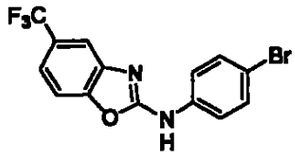
N-(4-Bromophenyl)-*N*-(5-methyl-1,3-benzoxazol-2-yl)amine



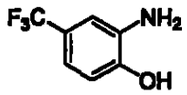
[283] In a 250-mL round-bottom flask, 1-bromo-4-isothiocyanatobenzene (4.28 g, 20 mmol) and 2-amino-4-methyl-phenol (2.46 g, 20 mmol) were stirred in 120 mL ethanol at rt overnight. The formation of *N*-(4-bromophenyl)-*N'*-(2-hydroxy-5-methylphenyl)thiourea was confirmed by LC-MS. To the mixture, 1.5 eq. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) was added, and the reaction was stirred at rt for another 2 h. The reaction mixture was then heated at reflux for 6 h. The mixture was cooled to rt and the solvent was removed under reduced pressure. The solid was dissolved in EtOAc and washed with 2 N aqueous HCl and H_2O. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The solid obtained was ultrasonicated in 30 mL ether and filtered to give the desired compound (3.64 g, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1 H), 7.70 (m, 2 H), 7.55 (m, 2 H), 7.35 (d, 1 H), 7.25 (s, 1 H), 6.95 (d, 1 H), 2.40 (s, 3 H). LC-MS *m/z* 303.3 (MH^+), ret. time 3.46 min.

[284] Intermediate NN

N-(4-Bromophenyl)-5-(trifluoromethyl)-1,3-benzoxazol-2-amine

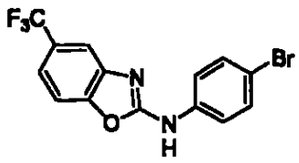


[285] 2-Amino-4-(trifluoromethyl)phenol



[286] Step 1. To a suspension of palladium hydroxide (3.05 g, 21.7 mmol) in methanol was added a methanol solution of 2-nitro-4-(trifluoromethyl)phenol (1.00 g, 4.8 mmol) followed by solid ammonium formate (3.04 g, 48.3 mmol). The mixture was heated at 85°C and monitored by TLC. The completed reaction was allowed to cool to rt and was filtered through a pad of Celite®, washing with ethyl acetate. The filtrate was concentrated under reduced pressure to provide the title compound (0.58 g, 67%). LC-MS *m/z* 178.1 (MH^+), retention time 0.55 minutes.

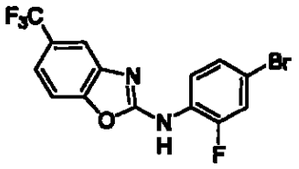
[287] N-(4-Bromophenyl)-5-(trifluoromethyl)-1,3-benzoxazol-2-amine



[288] Step 2. 2-Amino-4-(trifluoromethyl)phenol (250 mg, 1.41 mmol) and 1-bromo-4-isothiocyanatobenzene (302 mg, 1.41 mmol) were stirred in ethyl alcohol at ambient temperature for 18 h. The flask was charged with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) (405 mg, 2.12 mmol), and the mixture was stirred for 2 h before being heated at reflux overnight. The reaction was allowed to cool to rt and was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with 2 N aqueous hydrochloric acid solution and water, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with 85:15 hexanes/ethyl acetate to provide the title compound (315 mg, 62%). LC-MS *m/z* 357.1 (MH^+), retention time 4.20 minutes.

[289] **Intermediate QQ**

N-(4-Bromo-2-fluorophenyl)-5-(trifluoromethyl)-1,3-benzoxazol-2-amine



[290] 2-Amino-4-(trifluoromethyl)phenol (580 mg, 3.25 mmol) and 4-bromo-2-fluoro-1-isothiocyanatobenzene (750 mg, 3.25 mmol) were stirred in ethyl alcohol at ambient temperature for 18 h. The flask was charged with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) (405 mg, 2.12 mmol), and the mixture was stirred for 2 h before being heated at reflux overnight. The reaction was allowed to cool to rt and was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with 2 N aqueous hydrochloric acid solution and water, dried (Na_2SO_4), and concentrated *in vacuo*. The crude material was suspended in ether, sonicated, and the resulting solid was collected by filtration to provide the title compound (214 mg, 18%). LC-MS *m/z* 375.1 (MH^+), retention time 3.70 minutes.

[291] In a similar manner to the procedures described above, the following *N*-(4-bromophenyl)-*N*-(1,3-benzoxazol-2-yl)amines were prepared from the appropriate 4-bromo-1-isothiocyanatobenzene and 2-aminophenol:

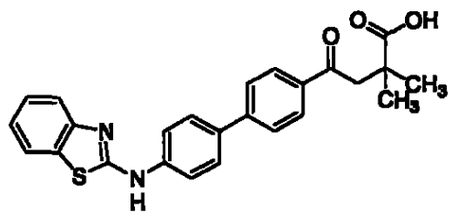
(a) *N*-(4-bromo-2-fluorophenyl)-*N*-(5-methyl-1,3-benzoxazol-2-yl)amine (LC-MS *m/z* 321.2 (MH^+), ret. time 3.69 min);

(b) *N*-(4-bromophenyl)-*N*-(6-methyl-1,3-benzoxazol-2-yl)amine (LC-MS *m/z* 303.2 (MH^+), ret. time 3.49 min).

Preparation of Compounds of Formula (I)

[292] **Example 1**

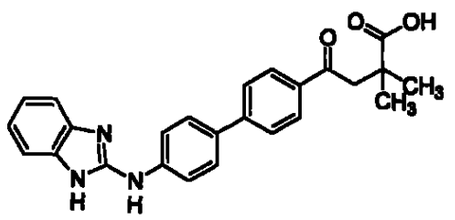
4-[4'-(1,3-Benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid



[293] In a 8-mL screw-cap vial, a mixture of methyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate (60 mg, 0.19 mmol) and 2-chloro-1,3-benzothiazole (40 mg, 0.23 mmol) in 3 mL n-butanol were heated at 90°C overnight. The formation of methyl 4-[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoate was monitored by LC-MS. The solvent was removed under reduced pressure. The residue was dissolved in 2 mL tetrahydrofuran/dioxane (1:1), and 3 equivalents of 1 *N* aqueous sodium hydroxide was added to the solution. The mixture was shaken at rt overnight and then at 50°C for 2 h. The progress of the hydrolysis reaction was monitored by LC-MS. A solution of 1N aqueous HCl (3.1 equivalents) was then added to the mixture, and the solvent was removed under reduced pressure. The residue was redissolved in 2 mL methanol and a minimum amount of *DMF*, and the product was isolated and purified by preparative reverse-phase HPLC (water/acetonitrile gradient, containing 0.1% TFA) to give 40 mg of 4-[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid (Yield: 45%). ^1H NMR (400 MHz, DMSO-d_6) δ 11.90 (bs, 1 H), 10.65 (s, 1 H), 8.00 (d, 2 H), 7.90 (d, 2 H), 7.80 (m, 5 H), 7.60 (d, 1 H), 7.35 (t, 1 H), 7.20 (t, 1 H), 3.30 (s, 2 H), 1.10 (s, 6 H); *LC-MS m/z* 431.2 (MH^+), ret. time 3.40 min.

[294] **Example 2**

4-[4'-(1*H*-Benzimidazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid

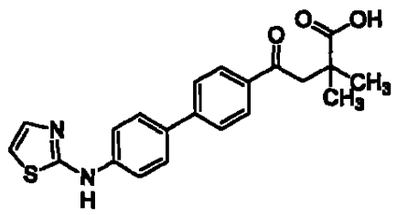


[295] This compound was prepared from methyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate (64 mg, 0.21 mmol) and 2-chloro-1H-benzimidazole (37.6 mg, 0.25 mmol) in a similar

manner to the method described for 4-[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid, providing 40.7 mg (48%) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (br s, 1 H), 11.05 (br s, 1 H), 8.05 (d, 2 H), 7.85 (m, 4 H), 7.65 (d, 2 H), 7.40 (m, 2 H), 7.10 (m, 2 H), 3.35 (s, 2 H), 1.25 (s, 6 H). *LC-MS m/z* 414.3 (MH^+), ret. time 2.27 min.

[296] **Example 3**

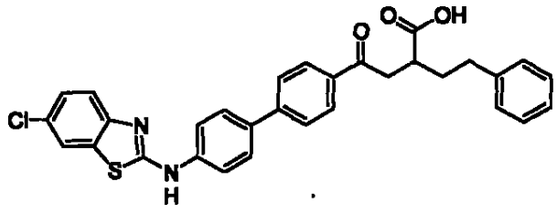
2,2-Dimethyl-4-oxo-4-[4'-(1,3-thiazol-2-ylamino)-1,1'-biphenyl-4-yl]butanoic acid



[297] This compound was prepared from methyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate (64 mg, 0.21 mmol) and 2-bromothiazole (41 mg, 0.25 mmol) in a similar manner to the method described for 4-[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid, providing 18.6 mg (24%) of the desired product. *LC-MS m/z* 381.4 (MH^+), ret. time 2.53 min.

[298] **Example 4**

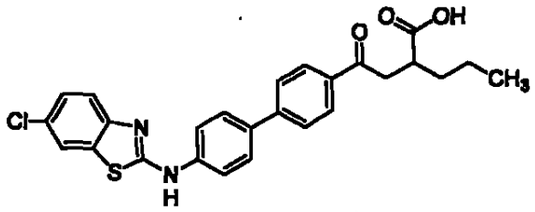
4-[4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-4-oxo-2-(2-phenylethyl)butanoic acid



[299] This compound was prepared from methyl 4-(4'-amino-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenylethyl)butanoate (78 mg, 0.20 mmol), 2,6-dichloro-1,3-benzothiazole (61.6 mg, 0.30 mmol) in a similar manner to the method described for 4-[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid, providing 26.7 mg (25%) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (br s, 1 H), 7.75-8.05 (m, 9 H), 7.60 (d, 1 H), 7.10-7.40 (m, 6 H), 3.50 (q, 1 H), 3.10 (m, 1 H), 2.85 (m, 1 H), 2.65 (m, 2 H), 1.80 (m, 2 H). LC-MS *m/z* 541.3 (MH^+), ret. time 4.07 min.

[300] **Example 5**

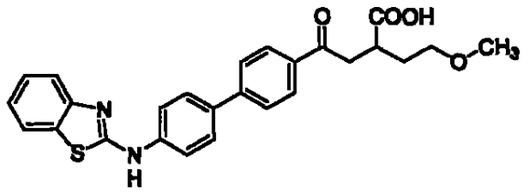
2-(2-[4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-2-oxoethyl)pentanoic acid



[301] This compound was prepared from methyl 2-[2-(4'-amino-1,1'-biphenyl-4-yl)-2-oxoethyl]-pentanoate (68 mg, 0.20 mmol) and 2,6-dichloro-1,3-benzothiazole (61.3 mg, 0.30 mmol) in a similar manner to the method described for 4-[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid, providing 17.2 mg (18%) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br s, 1 H), 10.75 (br s, 1 H), 7.75-8.05 (m, 9 H), 7.60 (d, 1 H), 7.35 (m, 1 H), 3.40 (q, 1 H), 3.10 (m, 1 H), 1.55 (m, 2 H), 1.35 (m, 2 H), 0.85 (t, 3 H). LC-MS *m/z* 479.3 (MH^+), ret. time 3.88 min.

[302] **Example 6**

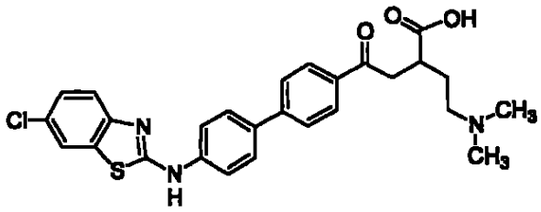
4-[4'-(1,3-Benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2-(2-methoxyethyl)-4-oxobutanoic acid



[303] To a solution of ethyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2-(2-methoxyethyl)-4-oxobutanoate (75 mg, 0.21 mmol) in butanol (4 mL), 2-chloro-benzothiazole (43 mg, 0.25 mmol) was added and the reaction mixture was heated at 90°C overnight. The solvent was removed by rotary evaporation, the residue was redissolved in DMF (1 mL), a solution of 1 N aqueous NaOH (0.63 mL, 0.63 mmol) was added, and the mixture was stirred at rt overnight. A solution of 1 N aqueous HCl (0.3 mL, 0.3 mmol) and methanol (5 mL) were added to the reaction mixture, and the crude product was purified by preparative reverse-phase HPLC (water/acetonitrile gradient, containing 0.1% TFA) to afford 4-[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2-(2-methoxyethyl)-4-oxobutanoic acid as a white solid (30 mg, 31%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.05 (d, 2 H), 7.95 (d, 2 H), 7.70 (m, 5 H), 7.60 (d, 1 H), 7.30 (t, 1 H), 7.15 (t, 2 H), 3.35 (m, 2 H), 3.25 (s, 3 H), 3.20 (m, 2 H), 2.90 (m, 1 H), 1.95-1.75 (m, 2 H); LC-MS ret. time 3.29 min (method 2), *m/z* 461.15 (MH^+).

[304] **Example 7**

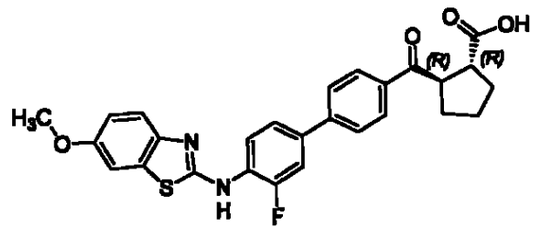
4-{4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2-[2-(dimethylamino)ethyl]-4-oxobutanoic acid



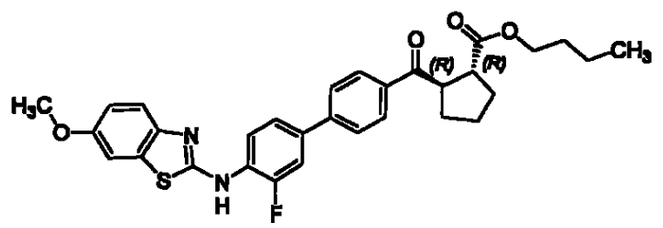
[305] This compound was prepared from methyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2-[2-(dimethylamino)ethyl]-4-oxobutanoate (60 mg, 0.17 mmol) and 2,6-dichloro-1,3-benzothiazole (51.8 mg, 0.25 mmol)) in a similar manner to the method described for 4-[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid, providing 14.1 mg (13%) of the desired product as the trifluoroacetate salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, 2 H), 7.70-8.10 (m, 8 H), 7.30 (m, 1 H), 3.60 (m, 1 H), 3.30-3.40 (m, 3 H), 3.10 (m, 1 H), 2.95 (s, 6 H), 2.20 (m, 1 H), 2.00 (m, 1 H). LC-MS *m/z* 508.1 (MH^+), ret. time 2.66 min.

[306] **Example 8**

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



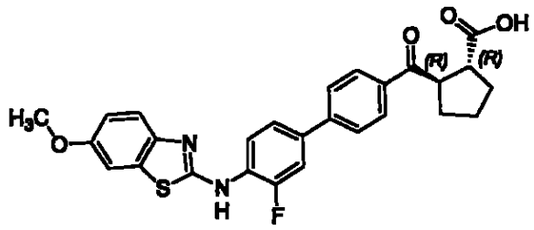
[307] Butyl (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylate



[308] Step 1. Methyl (1*R*,2*R*)-2-[(4'-amino-3'-fluoro-1,1'-biphenyl-4-yl)carbonyl]cyclopentanecarboxylate (462 mg, 1.35 mmol) was dissolved in n-butanol (15 mL), and 6-methoxy-2-(methylsulfonyl)-1,3-benzothiazole (162 mg, 0.8 mmol) and 4 M aqueous HCl (1.5 mL) were added.

The mixture was heated at 90°C for 5 h. An additional portion of 6-methoxy-2-(methylsulfonyl)-1,3-benzothiazole (162 mg, 0.8 mmol) was added, and the mixture was stirred overnight at 90°C. Solvent was then removed by rotary evaporation, and the residue was purified by flash chromatography (Biotage Flash 40 M, 3:1 hexane/EtOAc) to afford butyl (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylate (480 mg, 65%). LC-MS ret. time 4.36 min, *m/z* 547.3 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ: 0.85 (t, 3H), 1.25-1.35 (m, 2H), 1.40-1.58 (m, 2H), 1.74-1.84 (m, 3H), 1.91-1.96 (m, 1H), 2.11-2.20 (m, 2H), 3.40-3.46 (m, 1H), 3.84 (s, 3H), 4.03 (t, 2H), 6.81-6.87 (m, 1H), 6.98 (dd, 1H), 7.18 (d, 1H), 7.40-7.52 (m, 2H), 7.64 (d, 2H), 8.14 (d, 2H), 8.42 (t, 1H).

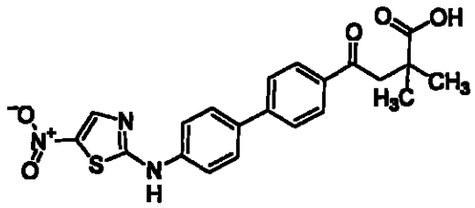
[309] (1*R*,2*R*)-2-({3'-Fluoro-4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-carbonyl)cyclopentanecarboxylic acid



[310] Step 2. To a solution of butyl (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-methoxy-1,3-benzothiazol-2-yl)-amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylate in methanol (8 mL) was added 1 N aqueous sodium hydroxide (6.15 mL), and the mixture was stirred at 50°C overnight. The solvent was then removed by rotary evaporation. Water (5 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The aqueous layer was then treated with 1 N aqueous HCl to adjust the acidity to pH 2, and then extracted with ethyl acetate. The organic phase was evaporated under reduced pressure, and the residue was purified by flash chromatography (Biotage Flash 40S, 6:1 EtOAc/hexane) to afford (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid (129 mg, 30%, 89% ee). LC-MS ret. time 3.56 min, *m/z* 491.3 (MH^+); ^1H NMR (300 MHz, DMSO-d_6) δ 1.58-1.84 (m, 4H), 1.96-2.01 (m, 1H), 2.14-2.17 (m, 1H). 3.22 (q, 1H), 3.77 (s, 3H), 4.02-4.10 (q, 1H), 6.94 (dd, 1H), 7.46 (d, 1H), 7.53 (d, 1H), 7.65-7.76 (m, 2H), 7.86 (d, 2H), 8.04 (d, 2H), 8.72 (t, 1H), 10.33 (br s, 1H).

[311] **Example 9**

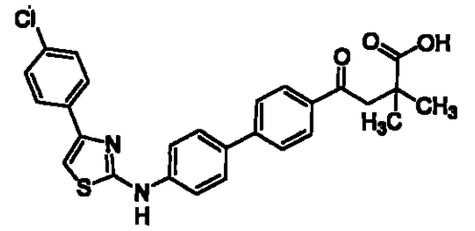
2,2-Dimethyl-4-{4'-[(5-nitro-1,3-thiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxobutanoic acid



[312] In a 8-mL screw-cap vial, a mixture of 4-(4'-amino-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoic acid (60 mg, 0.20 mmol) and 2-bromo-5-nitro-1,3-thiazole (63.3 mg, 0.30 mmol) in 4 mL n-butanol was heated at 90°C overnight. The solvent was removed under reduced pressure. The mixture was dissolved in 5 mL 1:4 MeOH/DMF and purified by reverse-phase HPLC to provide 8.9 mg (10%) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (br s, 1 H), 8.50 (s, 11 H), 7.70-8.05 (m, 8 H), 3.15 (d, 1 H), 1.25 (s, 6 H); LC-MS *m/z* 426.2 (MH^+), ret. time 3.12 min.

[313] **Example 10**

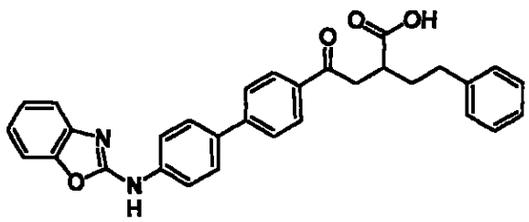
4-(4'-{[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]amino}-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoic acid



[314] In a 8-mL screw-cap vial, a mixture of 4-(4'-amino-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoic acid (60 mg, 0.20 mmol) and 2-(4-chlorophenyl)-2-oxoethyl thiocyanate (64 mg, 0.30 mmol) in 4 mL n-butanol was heated at 90°C overnight. The solvent was removed under reduced pressure. The mixture was dissolved in 5 mL 1:4 MeOH/DMF and purified by reverse-phase HPLC to provide 6.8 mg (7%) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (br s, 1 H), 10.50 (s, 1 H), 7.75-8.00 (m, 10 H), 7.50 (m, 3 H), 3.30 (m, 2 H), 1.05 (s, 6 H); LC-MS *m/z* 491.2 (MH^+), ret. time 3.83 min.

[315] **Example 11**

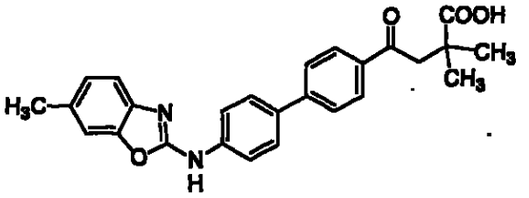
4-[4'-(1,3-Benzoxazol-2-ylamino)-1,1'-biphenyl-4-yl]-4-oxo-2-(2-phenylethyl)butanoic acid



[316] A solution of ethyl 4-(4'-amino-1,1'-biphenyl-4-yl)-4-oxo-2-(2-phenylethyl)butanoate (100 mg, 0.25 mmol) and 2-chlorobenzoxazole (38.3 mg, 0.25 mmol) in toluene (1.0 mL) was heated at reflux for 16 h. Solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane. The solution was washed with water, solvent was again removed under reduced pressure, and the residue was dissolved in methanol (1 mL) and tetrahydrofuran (1 mL). A 1 N aqueous solution of sodium hydroxide (0.77 mL, 0.77 mmol) was added, and the mixture was stirred at rt for 16 h and then concentrated under reduced pressure. The residue was purified by preparative reverse-phase HPLC (water/acetonitrile gradient, containing 0.1% TFA) to afford 4-[4'-(1,3-benzoxazol-2-ylamino)-1,1'-biphenyl-4-yl]-4-oxo-2-(2-phenylethyl)butanoic acid (40 mg, 33% yield). *LC-MS* ret. time 4.14 min, *m/z* 519.5 (MH^+); ^1H NMR (300 MHz, DMSO-d_6) δ 1.82-1.90 (m, 2H), 2.68 (m, 2H), 2.80-2.85 (m, 1H), 3.16 (dd, 1H), 3.41 (m, 1H), 7.10-7.30 (m, 8H), 7.48 (t, 2H), 7.78-7.86 (m, 4H), 7.89 (d, 2H), 8.02 (d, 2H), 10.83 (br s, 1H).

[317] **Example 12**

2,2-Dimethyl-4-{4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxobutanoic acid

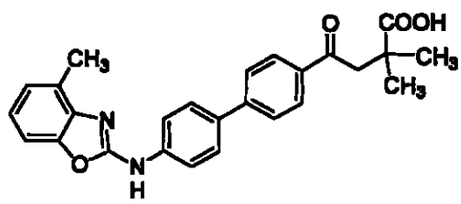


[318] To a solution of methyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate (74 mg, 0.24 mmol) in dichloroethane (3 mL), 6-methyl-2-(methylsulfinyl)-1,3-benzoxazole (50 mg, 0.24 mmol) was added, and the mixture was heated at 85°C overnight. The solvent was removed by rotary evaporation, and the residue was redissolved in DMF (5 mL). A solution of 1 N aqueous NaOH (0.72 mL, 0.72 mmol) was added, and the mixture was heated at 65°C overnight. A solution of 1 N aqueous HCl (0.24 mL, 0.24 mmol) and methanol (5 mL) were added to the reaction mixture and the crude product was purified by preparative reverse-phase HPLC (water/acetonitrile gradient, containing 0.1% TFA) to afford 2,2-dimethyl-4-{4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-

biphenyl-4-yl}-4-oxobutanoic acid as a white solid (32.6 mg, 32.1 %). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 – 7.50 (m, 8 H), 7.30 (d, 2 H), 7.05 (d, 1 H), 3.30 (s, 2 H), 2.50 (s, 3 H), 1.10 (s, 6 H); LC-MS ret. time 3.53 min (method 2), *m/z* 429.17 (MH^+).

[319] **Example 13**

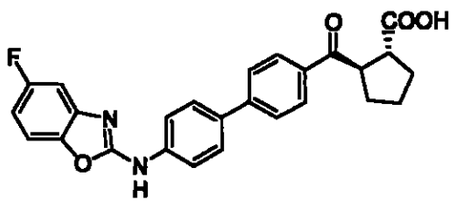
2,2-Dimethyl-4-{4'-[(4-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxobutanoic acid



[320] To a solution of methyl 4-(4'-amino-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoate (74 mg, 0.24 mmol) in dichloroethane (3 mL), 4-methyl-2-(methylsulfonyl)-1,3-benzoxazole (50 mg, 0.24 mmol) was added, and the mixture was heated at 85°C overnight. The solvent was removed by rotary evaporation and the residue was redissolved in DMF (5 mL). A solution of 1 N aqueous NaOH (0.72 mL, 0.72 mmol) was added, and the mixture was heated at 65°C overnight. A solution of 1 N aqueous HCl (0.24 mL, 0.24 mmol) and methanol (5 mL) was added to the reaction mixture and the crude product was purified by preparative reverse-phase HPLC (water/acetonitrile gradient, containing 0.1% TFA) to afford 2,2-dimethyl-4-{4'-[(4-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxobutanoic acid as a white solid (32.6 mg, 32.1%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00-7.80 (m, 8 H), 7.30 (d, 1 H), 7.05 (d, 2 H), 3.30 (s, 2 H), 2.50 (s, 3 H), 1.10 (s, 6 H); LC-MS ret. time 3.77 min (method 2), *m/z* 429.2 (MH^+).

[321] **Example 14**

***trans*-2-({4'-[(5-Fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid**

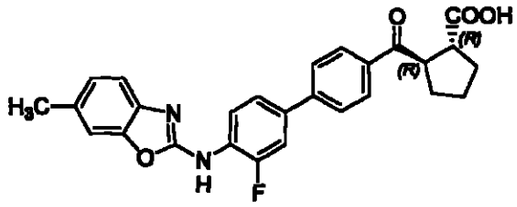


[322] To a solution of methyl *trans*-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]cyclopentanecarboxylate (100 mg, 0.31 mmol) in dichloroethane (3 mL), 5-fluoro-2-(methylsulfonyl)-1,3-benzoxazole (80 mg, 0.37 mmol) was added and the mixture was heated at 85°C overnight. The solvent was removed by rotary evaporation, and the residue was redissolved in DMF (5 mL). A

solution of 1 N aqueous NaOH (0.93 mL, 0.93 mmol) was added and the mixture was heated at 65°C overnight. A solution of 1 N aqueous HCl (0.31 mL, 0.31 mmol) and methanol (5 mL) were added to the reaction mixture, and the crude product was purified by preparative reverse-phase HPLC (water/acetonitrile gradient, containing 0.1% TFA) to afford 2-({4'-[(5-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid as a white solid (43.7 mg, 31.4%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.05 (d, 2 H), 7.90-7.80 (m, 6 H), 7.50 (m, 1 H), 7.30 (m, 1 H), 6.95 (m, 1 H), 4.05 (m, 1 H), 3.20 (m, 1 H), 2.20 (m, 1 H), 1.95 (m, 1 H), 1.80-1.60 (m, 4 H); LC-MS ret. time 3.66 min (method 2), *m/z* 445.1 (MH^+).

[323] **Example 15**

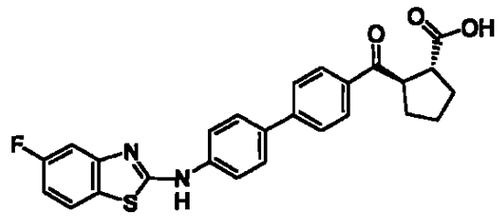
(1*R*,2*R*)-2-({3'-Fluoro-4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid



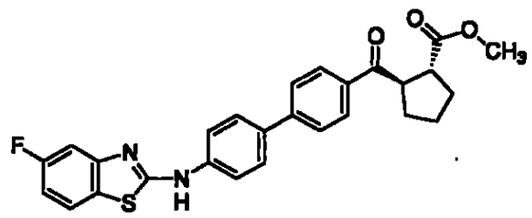
[324] To a solution of methyl (1*R*,2*R*)-2-[(4'-amino-3'-fluoro-1,1'-biphenyl-4-yl)carbonyl]-cyclopentanecarboxylate (800 mg, 2.34 mmol, 78% ee) in dichloroethane (15 mL), 6-methyl-2-(methylsulfonyl)-1,3-benzoxazole (891 mg, 4.22 mmol) was added, and the mixture was heated at 85°C overnight. The solvent was removed by rotary evaporation, and the residue was purified by using a Biotage QuadUV flash chromatography system (eluant: 80:20 hexane/EtOAc) to give methyl (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentanecarboxylate (472 mg). This ester intermediate was redissolved in 1:1 dioxane/THF (20 mL), a solution of 1 N aqueous NaOH (7.02 mL, 7.02 mol) was added, and the mixture was heated at 50°C overnight. The solvent was removed by rotary evaporation, and water (20 mL) and EtOAc (40 mL) were added to the residue. The aqueous layer was separated, acidified to pH 5 by the addition of 1 N aqueous HCl, and then extracted with EtOAc (2 x 60 mL). The combined organic phases were washed with saturated NaCl and dried (Na_2SO_4). The solvent was removed by rotary evaporation and the residue was redissolved in DMF (10 mL) and methanol (20 mL). The crude product was purified by preparative reverse-phase HPLC (water/acetonitrile gradient, containing 0.1% TFA) to afford (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid as an off-white solid (161 mg, 15% yield, 80% ee). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (m, 1 H), 8.00-7.60 (m, 6 H), 7.30 (d, 2 H), 7.00 (d, 1 H), 4.05 (m, 1 H), 3.20 (m, 1 H), 2.40 (s, 3 H), 2.20 (m, 1 H), 1.95 (m, 1 H), 1.80-1.60 (m, 4 H); LC-MS ret. time 3.57 min, *m/z* 459.3 (MH^+).

[325] **Example 16**

***trans*-2-({4'-[(5-Fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid**

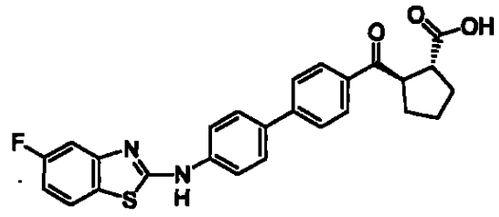


[326] Methyl *trans*-2-({4'-[(5-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentanecarboxylate



[327] Step 1. 2-Chloro-5-fluoro-1,3-benzothiazole (29 mg, 0.16 mmol) and methyl *trans*-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]cyclopentanecarboxylate (50 mg, 0.16 mmol) were combined in 1-butanol. The solution was treated with 4 M HCl in dioxane (4 μL, 0.016 mmol) and heated at 90°C for 18 h. The reaction mixture was concentrated under reduced pressure. The residue was suspended in methanol, and the resulting solid was collected by filtration and dried *in vacuo*. The title compound was obtained as a pale yellow solid (55 mg, 77 %); LC-MS *m/z* 475.3 (MH^+), retention time 3.97 minutes.

[328] *trans*-2-({4'-[(5-Fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentanecarboxylic acid

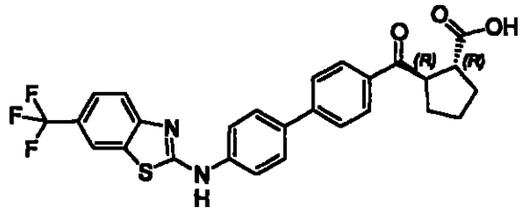


[329] Step 2. A solution of 1 N aqueous sodium hydroxide solution (1 mL) was added to *trans*-methyl 2-({4'-[(5-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylate (55 mg, 0.12 mmol) in THF (2 mL). Methanol was added until the mixture became homogeneous, and the resulting solution was heated at 60°C for 1 h. The reaction was concentrated under reduced pressure to remove excess solvents, and the residue was partitioned between water and

chloroform/isopropanol (4:1). The aqueous layer was adjusted to pH 2 by addition of aqueous phosphoric acid solution, with stirring. The organic layer was then separated, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was suspended in acetone, and the resulting solid was collected by filtration and dried *in vacuo* to provide the title compound (45 mg, 84%). ^{1}H NMR (300 MHz, acetone-d_6) δ 10.40–10.10 (br s, 1 H), 8.15 (d, 2 H), 8.01 (d, 2 H), 7.87–7.82 (m, 5 H), 7.41 (dd, 1 H), 7.05-6.95 (m, 1 H), 4.26–4.17 (m, 1 H), 3.43-3.34 (m, 1 H), 2.31–2.23 (m, 1 H), 1.98–1.70 (m, 5 H); LC-MS *m/z* 461.3 (MH^+), retention time 3.56 minutes.

[330] **Example 17**

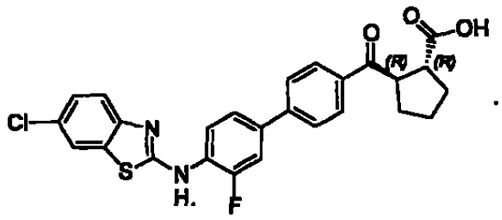
(1*R*,2*R*)-2-[(4'-{[6-(Trifluoromethyl)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentanecarboxylic acid



[331] A mixture of methyl (1*R*,2*R*)-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylate (150 mg, 0.464 mmol) and 2-chloro-6-(trifluoromethyl)-1,3-benzothiazole(132 mg, 0.557 mmol) was diluted with *n*-butanol (3 mL) and treated with a catalytic amount of 4 M HCl in dioxane. The suspension was heated at 90°C overnight. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel, eluting with a gradient from 9:1 to 3:2 hexanes / ethyl acetate. The product obtained was suspended in diethyl ether, and the resulting solid was collected by filtration and washed with additional diethyl ether and hexanes. LC-MS for the n-butyl ester: LC-MS *m/z* 567.3 (MH^+), 4.67 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14-8.10 (m, 3 H), 7.80-7.71 (m, 6 H), 7.62 (d, 2 H), 4.17-4.13 (m, 1 H), 4.09-4.04 (m,2 H), 3.51-3.41 (m, 1 H), 2.21-2.13 (m, 2 H), 1.97-1.90 (m, 1 H), 1.81-1.78 (m, 3 H), 1.58-1.51 (m, 2 H), 1.35-1.28 (m, 2 H),1.23-1.18 (t, 3 H), 0.88 (t, 2 H). The off-white solid was diluted with methanol (2 mL) and tetrahydrofuran (2 mL) and treated with 2 M aqueous sodium hydroxide solution (2 mL). The solution was stirred overnight at rt. The mixture was acidified by the addition of an excess of 2 M aqueous hydrochloric acid solution. The acidic solution was extracted with ethyl acetate. The organic phases were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was suspended in methanol and the resulting solids were removed by filtration. The filtrate, which contained the product, was concentrated under reduced pressure to provide the title compound as a pale orange solid (30 mg, 13% overall yield). ^{1}H NMR (tetrahydrofuran-d_8) δ 10.85 (s, 1 H), 8.11-8.07 (m, 3 H), 7.96-7.91 (m, 2 H), 7.79-7.71 (m, 5 H), 7.63-7.59 (dd, 1 H), 4.18 (q, 1 H), 3.37 (q, 1 H), 2.2-1.77 (m, 6 H); LC-MS *m/z* 511.3 (MH^+), retention time 4.27 minutes.

[332] **Example 18**

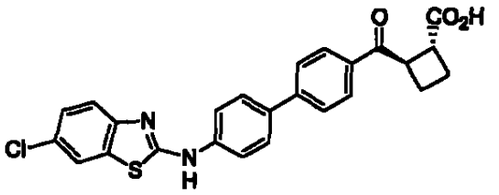
(1*R*,2*R*)-2-({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid



[333] A suspension of *N*-(4-iodo-2-fluorophenyl)-6-chloro-1,3-benzothiazol-2-amine (200 mg, 0.49 mmol), bis(pinacolato)diboron (130 mg, 0.52 mmol), KOAc (150 mg, 1.48 mmol), and $PdCl_2$(dppf) (30 mg, 0.04 mmol) in *DMF* (5.0 mL) was degassed by bubbling a flow of nitrogen for 30 minutes. The reaction mixture was heated under nitrogen at 85°C for 3 h. After the mixture was cooled to rt, (1*R*,2*R*)-2-(4-bromobenzoyl)cyclopentanecarboxylic acid (140 mg, 0.49 mmol, >99%ee), Cs_2CO_3 (400 mg, 1.23 mmol) and $PdCl_2$(dppf) (30 mg, 0.04 mmol) were added, and the reaction mixture was heated at 85°C under nitrogen for 3 h. TLC analysis showed little starting materials remaining. The reaction mixture was cooled to rt, and diluted with water (50 mL). After the mixture was filtered through a pad of Celite®, 1 N HCl was added to the filtrate to adjust the acidity to pH<3. The solid that formed was collected by filtration, then dissolved in EtOAc (50 mL), and the resulting solution was dried over Na_2SO_4. Removal of solvent and drying *in vacuo* provided the desired product (120 mg, 60%, >99% ee). *LC-MS m/z* 495.3 (MH^+), retention time 4.01 min.

[334] **Example 19**

***trans*-2-({4'-[(6-Chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclobutanecarboxylic acid**

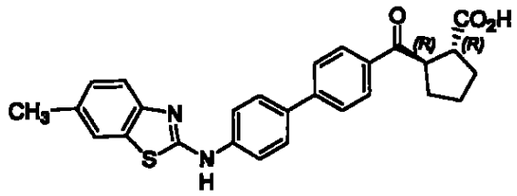


[335] To a solution of methyl *trans*-2-[(4'-amino-1, 1'-biphenyl-4-yl) carbonyl]cyclobutane-carboxylate (100 mg, 0.32 mmol) in n-butanol (15 mL) was added 2,6-dichloro-1,3-benzothiazole (396 mg, 1.94 mmol), and the resulting reaction mixture was heated at 90°C overnight. The mixture was evaporated to dryness and the residue was brought up in MeOH. Then 1 N aqueous NaOH (1.0 mL, 1.0 mmol) was added to the suspension, and the reaction mixture was stirred at 50°C overnight. The reaction mixture was concentrated, and the residue was suspended in water. Concentrated HCl was added to adjust the acidity to pH 1, and the precipitate that formed was

collected by filtration, washed with water and MeOH, and dried in a vacuum oven to give *trans*-2-({4'-[(6-chloro-1, 3-benzothiazol-2-yl) amino]-1,1'-biphenyl-4-yl}carbonyl)cyclobutanecarboxylic acid (16 mg, 10%). LC-MS ret. time 3.69; *m/z* 463.1 (MH^+); ^1H NMR (400 MHz, DMSO-d_6) δ 2.01-2.23 (m, 3H), 2.32 (m, 1H), 3.43 (m, 1H), 4.32 (m, 1H), 7.35 (m, 1H), 7.31 (m, 1H), 7.62 (d, 1H), 7.81 (m, 4H), 7.90 (d, 2H), 7.98 (m, 3H), 10.77 (s, 1H), 12.29 (s, 1H).

[336] **Example 20**

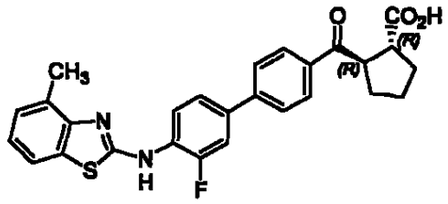
***trans*-2-({4'-[(6-Methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl} carbonyl)cyclopentanecarboxylic acid**



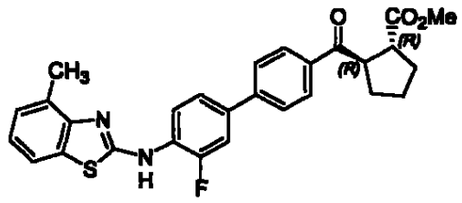
[337] N-(4-iodophenyl)-6-methyl-1,3-benzothiazol-2-amine (0.28 g, 0.78 mmol) and methyl *trans*-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl]cyclopentanecarboxylate (0.25 g, 0.71 mmol) were combined in a dry flask under argon. Toluene (15 mL), EtOH (6 mL), and saturated aqueous $NaHCO_3$ (2 mL) were then added, and the resulting solution was degassed by bubbling a flow of argon for 30 minutes. Then [1,1'-bis(diphenylphosphino)-ferrocene]dichloro-palladium (II), complex with dichloromethane (1:1) (57 mg, 0.07 mmol) was added, and the resulting mixture was heated at 85°C for 16 h. The reaction mixture was then diluted with EtOAc and filtered through a Celite® pad. The solvent was removed by rotary evaporation and the residue was brought up in MeOH. Then 1 N aqueous NaOH (2.0 mL, 2.0 mmol) was added to the suspension, and the reaction mixture was stirred at 50°C overnight. The reaction mixture was concentrated under reduced pressure and the residue was suspended in water. Concentrated HCl was added to adjust the acidity to pH 1, and the suspension was extracted with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate, passed through a pad of silica gel, and concentrated *in vacuo*. The residue was brought up in EtOAc and the precipitate was collected by filtration, washed with EtOAc, MeOH, and DCM, and dried in a vacuum oven to afford *trans*-2-({4'-[(6-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentanecarboxylic acid (0.24 g, 19%). LC-MS ret. time 3.57; *m/z* 457.3 (MH^+); ^1H NMR (400 MHz, DMSO-d_6) δ 1.57-1.86 (m, 4H), 2.00 (m, 1H), 2.17 (m, 1H), 2.37 (s, 3H), 3.22 (q, 1H), 4.08 (q, 1H), 7.14 (m, 1H), 7.51 (d, 1H), 7.61 (s, 1H), 7.80 (m, 3H), 7.89 (d, 2H), 8.05 (d, 2H), 10.58 (s, 1H), 12.19 (s, 1H).

[338] **Example 21**

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

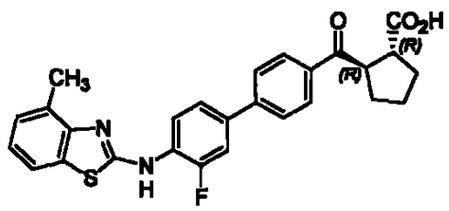


[339] Methyl (R,R)-*trans*-2-({3'-fluoro-4'-[(4-methyl-1, 3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylate



[340] Step 1. N-(4-bromo-2-fluorophenyl)-4-methyl-1,3-benzothiazol-2-amine (0.10 g, 0.30 mmol) and methyl (R,R)-*trans*-2-[4-(4,4,5,5-tetramethyl-1, 3,2-dioxaborolan-2-yl) benzoyl] cyclopentanecarboxylate (0.19 g, 0.54 mmol, 94% ee) were combined in a dry flask under argon. Toluene (25 mL), EtOH (8 mL), and saturated aqueous $NaHCO_3$ (5 mL) were added, and the resulting suspension was degassed by bubbling with a flow of argon for 30 minutes. Then [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (40 mg, 0.05 mmol) was added, and the resulting mixture was heated at 85°C for 16 h. The reaction mixture was then diluted with EtOAc and the layers were separated. The organic layer was washed with aqueous HCl (1.0 M), water and brine, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (Biotage Flash 25S) using 10 to 15% ethyl acetate in hexane to afford methyl (*R,R*)-*trans*-2-({3'-fluoro-4'-[(4-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylate (0.09 g, 37%). ^1H NMR (400 MHz, CD_2Cl_2) δ 1.75-1.86 (m, 3H), 1.93 (m, 1H), 2.12-2.26 (m, 2H), 2.69 (s, 3H), 3.45 (q, 1H), 3.66 (s, 3H), 4.12 (q, 1H), 7.14 (t, 1H), 7.22 (d, 1H), 7.50 (m, 2H), 7.56 (t, 2H), 7.73 (d, 2H), 8.07 (d, 2H), 8.72 (t, 1H).

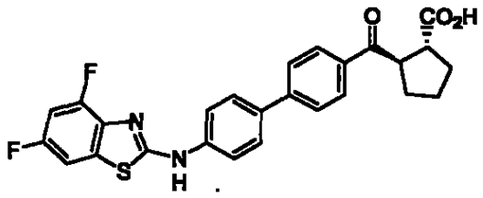
[341] (*R,R*)-*trans*-2-({3'-fluoro-4'-[(4-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-carbonyl)cyclopentanecarboxylic acid



[342] Step 2. Methyl (*R,R*)-*trans*-2-({3'-fluoro-4'-[(4-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylate (90 mg, 0.18 mmol) was brought up in MeOH. Then 1 N aqueous NaOH (1.0 mL, 1.0 mmol) was added to the suspension, and the reaction mixture was stirred at 50°C overnight. The reaction mixture was concentrated, and the residue was suspended in water. Conc. HCl was added to adjust the acidity to pH 1, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated to give (*R,R*)-*trans*-2-({3'-fluoro-4'-[(4-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid (32 mg, 36%). LC-MS ret. time 3.97; *m/z* 475.3 (MH^+); ^1H NMR (400 MHz, DMSO-d_6) δ 1.56-1.83 (m, 4H), 2.00 (m, 1H), 2.16(m, 1H), 2.57 (s, 3H), 3.22 (q, 1H), 4.09 (q, 1H), 7.07 (t, 1H), 7.16 (d, 1H), 7.63 (m, 1H), 7.70 (m, 1H), 7.75 (m, 1H), 7.88 (d, 2H), 8.05 (d, 2H), 8.84 (t, 1H), 10.47 (s, 1H).

[343] **Example 22**

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

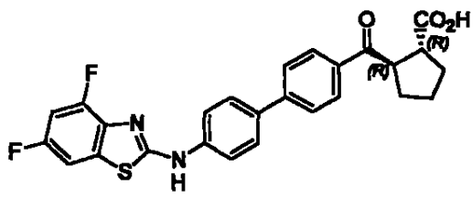


[344] To a solution of racemic methyl *trans*-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]cyclobutane-carboxylate (250 mg, 0.77 mmol) in n-butanol (15 mL) was added 2-chloro-4,6-difluoro-1,3-benzothiazole (318 mg, 1.55 mmol), and the resulting solution was heated at 90°C overnight. The mixture was then evaporated to dryness under reduced pressure, and the residue was brought up in MeOH. Then 1 N aqueous NaOH (8.0 mL, 8.0 mmol) was added to the suspension, and the reaction mixture was stirred at 50°C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was suspended in water. Conc. HCl was added to adjust the acidity to pH 1, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was brought up in MeOH, and the

precipitate was collected by filtration, washed with MeOH, EtOAc, and DCM, and dried in a vacuum oven to afford racemic *trans*-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-carbonyl)cyclopentanecarboxylic acid (160 mg, 43%). *LC-MS* ret. time 4.12; *m/z* 479.3 (MH^+); ^1H NMR (400 MHz, DMSO-d_6) δ 1.55-1.86 (m, 4H), 2.00 (m, 1H), 2.18 (m, 1H), 3.22 (q, 1H), 4.01 (q, 1H), 7.28 (m, 1H), 7.65 (m, 1H), 7.82 (m, 4H), 7.88 (d, 2H), 8.05 (d, 2H), 10.83(s, 1H), 12.23 (s, 1H).

[345] **Example 23**

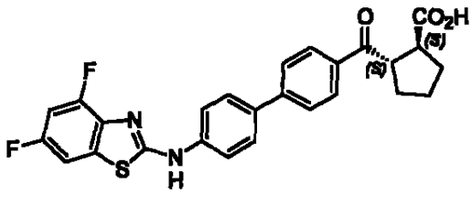
(1*R*,2*R*)-2-({4'-[(4,6-Difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid



[346] Racemic *trans*-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl) amino]-1,1'-biphenyl-4-yl}-carbonyl)cyclopentanecarboxylic acid (140 mg, 0.29 mmol) was separated by chiral HPLC to afford (1*R*,2*R*)-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentanecarboxylic acid as the first-eluting enantiomer (13.2 mg, 9%, 99% ee). *LC-MS* ret. time 3.64; *m/z* 479.2 (MH^+); ^1H NMR (400 MHz, DMSO-d_6) δ 1.58-1.86 (m, 4H), 2.00 (m, 1H), 2.17 (m, 1H), 3.21 (q, 1H), 4.10 (q, 1H), 7.29 (m, 1H), 7.66 (m, 1H), 7.82 (m, 4H), 7.88 (d, 2H), 8.06 (d, 2H), 10.83 (s, 1H), 12.23 (s, 1H).

[347] **Example 24**

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

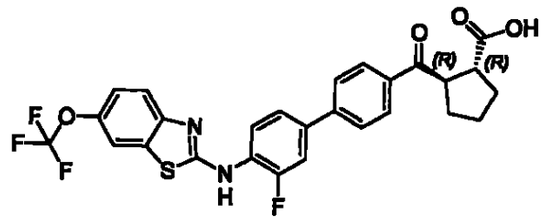


[348] Racemic *trans*-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-carbonyl)cyclopentanecarboxylic acid (140 mg, 0.29 mmol) was separated by chiral HPLC to afford (1*S*,2*S*)-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl) amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentanecarboxylic acid as the second-eluting enantiomer (23.8 mg, 17%, 74% ee). LC-MS ret. time 3.65; *m/z* 479.2 (MH^+); ^1H NMR (400 MHz, DMSO-d_6) δ 1.56-1.87 (m, 4H), 2.01 (m, 1H), 2.18

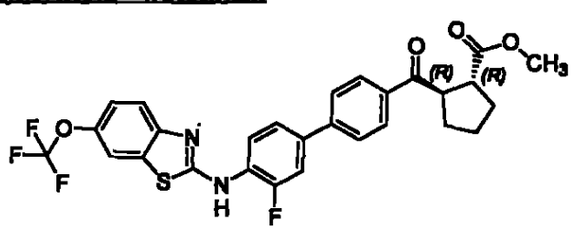
(m, 1H), 3.22 (q, 1H), 4.09 (q, 1H), 7.28 (m, 1H), 7.66 (m, 1H), 7.82 (m, 4H), 7.89 (d, 2H), 8.06 (d, 2H), 10.83 (s, 1H), 12.22 (s, 1H).

[349] **Example 25**

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



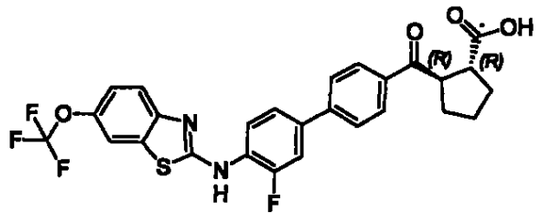
[350] Methyl (1*R*,2*R*)-2-[(3'-fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentanecarboxylate



[351] Step 1. In a 100 mL 3-neck round bottom flask, a mixture of methyl (1*R*,2*R*)-2-(4-bromobenzoyl)cyclopentanecarboxylate (3.11 g, 10 mmol, 94.5% ee), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (2.54 g, 10 mmol), and potassium acetate (2.94 g, 30 mmol) in 50 mL *N*,*N*-dimethylformamide was degassed by bubbling a flow of nitrogen gas for 30 minutes. Palladium (II) acetate (0.07 g, 0.30 mmol) was added to the reaction mixture, and the mixture was heated at 85°C for 3 h. The transformation of methyl (1*R*,2*R*)-2-(4-bromobenzoyl)cyclopentanecarboxylate to methyl (1*R*,2*R*)-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl]cyclopentanecarboxylate was confirmed by TLC analysis. The mixture was cooled to rt and poured into a separation funnel. Ethyl acetate (100 mL) and H_2O (100 mL) were added. The organic layer was washed with water (2 x 50 mL) and treated with Na_2SO_4 and activated charcoal. The mixture was filtered through a pad of silica gel, and the filtrate was concentrated under reduced pressure to provide methyl (1*R*,2*R*)-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl]cyclopentanecarboxylate as an oil. This oil was transferred to a 250-mL 3-neck round-bottom flask. To the flask, *N*-(4-bromo-2-fluorophenyl)-*N*-(6-trifluoromethoxy-1,3-benzothiazol-2-yl)amine (3.66 g, 9 mmol), 150 mL toluene, 60 mL ethanol, and 20 mL saturated aqueous $NaHCO_3$ were added. The mixture was degassed by bubbling nitrogen gas for 30 minutes. 1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) dichloromethane complex (0.82 g, 1.0 mmol) was added to the reaction mixture. The mixture was heated at 85°C

overnight. The workup procedure was then carried out in a similar to that described above. The filtrate was concentrated under reduced pressure and the solid residue was ultrasonicated in 100 mL acetonitrile for 30 minutes and filtered to give the desired compound as a white solid (2.59 g, 52%). LC-MS *m/z* 559.3 (MH^+), ret. time 4.75 min.

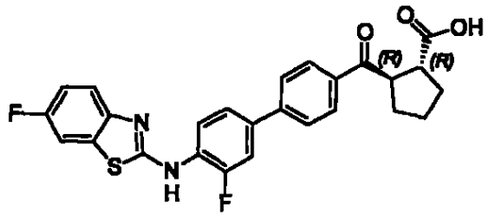
[352] (1*R*,2*R*)-2-({3'-Fluoro-4'-[(6-trifluoromethoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid



[353] Step 2. In 250-mL round-bottom flask, methyl (1*R*,2*R*)-2-[(3'-fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentanecarboxylate (2.53 g, 4.53 mmol) was dissolved in 100 mL of 1:1 THF/dioxane containing 5.0 molar equivalents of 1 N aqueous NaOH. The mixture was stirred at rt overnight. The mixture was concentrated under reduced pressure to a volume of about 20 mL. Ethyl acetate (100 mL), water (30 mL), and 5.1 molar equivalents of 1 N aqueous HCl were added to the mixture. The mixture was transferred to a separation funnel. The organic layer was washed with water (1 x 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The solid was ultrasonicated in 30 mL acetonitrile and filtered to give the desired compound as a white solid (1.96 g, 80%, 94.5% ee). ^1H NMR (400 MHz, DMSO-d_6) δ 12.20 (br s, 1 H), 10.60 (bs, 1 H), 8.70 (t, 1 H), 7.60-8.20 (m, 8 H), 7.30 (d, 1 H), 4.70 (q, 1 H), 3.20 (q, 1 H), 2.20 (m, 1 H), 2.00 (m, 1 H), 1.50-1.90 (m, 4 H); LC-MS *m/z* 545.3 (MH^+), ret. time 3.93 min.

[354] **Example 26**

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

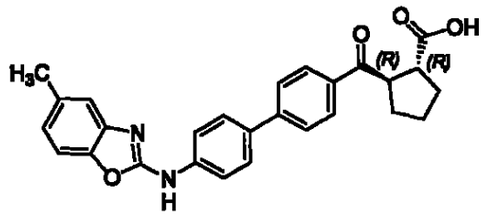


[355] *tert*-Butyl (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylate was prepared from *tert*-butyl (1*R*,2*R*)-2-(4-bromobenzoyl)-cyclopentanecarboxylate and *N*-(4-bromo-2-fluorophenyl)-*N*-(6-fluoro-1,3-benzothiazol-2-yl)amine in

a similar manner to that described above for methyl (1*R*,2*R*)-2-[(3'-fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentanecarboxylate. A solution of the *tert*-butyl ester (1.5 g, 2.81 mmol) in 2.0 mL TFA and 10 mL CH_2Cl_2 was stirred at rt overnight. After the solvent was removed by rotary evaporation, 50 mL EtOAc and 50 mL water were added. The organic layer was separated, washed with 50 mL water, and then dried over Na_2SO_4. After the solvent was removed by rotary evaporation, 5 mL EtOAc was added to the residue, followed by 5 mL hexanes. The precipitate that formed was collected by filtration to afford the desired product as a light yellow solid (1.0 g, 77%, 95.2% ee). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (br s, 1 H), 10.50 (bs, 1 H), 8.70 (t, 1 H), 7.60-8.10 (m, 8 H), 7.20 (t, 1 H), 4.10 (m, 1H), 3.20 (m, 1 H), 2.20 (m, 1 H), 2.00 (m, 1 H), 1.50-1.90 (m, 4 H); LC-MS *m/z* 479.3 (MH^+), ret. time 3.64 min.

[356] **Example 27**

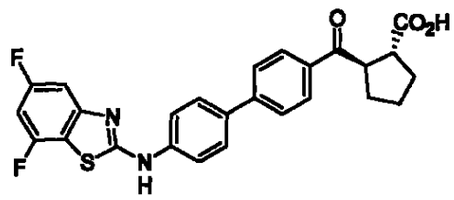
(1*R*,2*R*)-2-({4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid



[357] This compound was prepared from *N*-(4-bromophenyl)-*N*-(5-methyl-1,3-benzoxazol-2-yl)amine (0.50 g, 1.65 mmol), methyl (1*R*,2*R*)-2-(4-bromobenzoyl) cyclopentanecarboxylate (0.57 g, 1.83 mmol, 94.5% ee) in a similar manner to the method described for (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-trifluoromethoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid. Yield: 17%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1 H), 8.05 (d, 2 H), 7.75-7.90 (m, 6 H), 7.35 (d, 1 H), 7.25 (s, 1 H), 6.95 (d, 1 H), 4.05 (q, 1 H), 3.20 (s, 1 H), 2.40 (s, 3 H), 2.15 (m, 1 H), 2.00 (m, 1 H), 1.55-1.80 (m, 4 H). LC-MS *m/z* 441.3 (MH^+), ret. time 3.48 min.

[358] **Example 28**

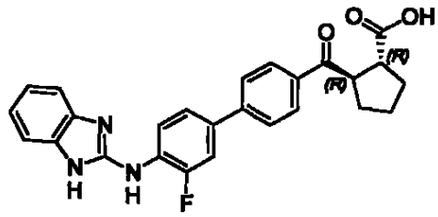
***trans*-2-({4'-[(5,7-Difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid**



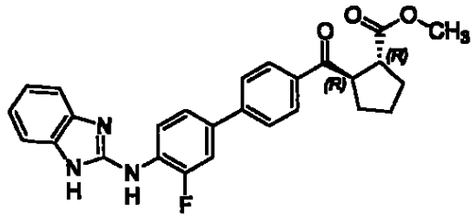
[359] To a solution of methyl *trans*-2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]cyclobutanecarboxylate (80 mg, 0.25 mmol) in n-butanol (8 mL) was added 2-chloro-5,7-difluoro-1,3-benzothiazole (102 mg, 0.49 mmol) and HCl (4.0 M in dioxane, 0.2 mL). The resulting reaction mixture was heated at 90°C overnight. The mixture was evaporated to dryness, and the residue was brought up in MeOH. Then 1 N aqueous NaOH (2.0 mL, 2.0 mmol) was added, and the reaction mixture was stirred at 50°C overnight. The reaction mixture was concentrated and the residue was suspended in water. Conc. HCl was added to adjust the acidity to pH 1, and the suspension was extracted with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was brought up in MeOH, and the precipitate was collected by filtration and dried under vacuum oven to afford *trans*-2-({4'-[(5,7-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid (65 mg, 58%). LC-MS ret. time 3.75; *m/z* 479.2 (MH^+). ^1H NMR (400 MHz, DMSO-d_6) δ 1.55-1.84 (m, 4H), 2.01 (m, 1H), 2.18 (m, 1H), 3.22 (q, 1H), 4.09 (q, 1H), 7.15 (m, 1H), 7.40 (m, 1H), 7.83 (m, 4H), 7.87 (d, 2H), 8.05 (d, 2H), 11.00 (s, 1H), 12.12 (s, 1H).

[360] **Example 29**

(1*R*,2*R*)-2-{[4'-(1*H*-benzimidazol-2-ylamino)-3'-fluoro-1,1'-biphenyl-4-yl]carbonyl}cyclopentanecarboxylic acid



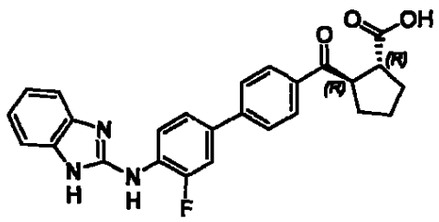
[361] Methyl (1*R*,2*R*)-2-{[4'-(1H-benzimidazol-2-ylamino)-3'-fluoro-1,1'-biphenyl-4-yl]carbonyl}-cyclopentanecarboxylate.



[362] Step 1. Methyl (1*R*,2*R*)-2-[(4'-amino-3'-fluoro-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylate (100 mg, 0.29 mmol, 80 %ee) and 2-chlorobenzimiazole (49 mg, 0.32 mmol) were combined in 1,4-dioxane (2 mL) and treated with one molar equivalent of 4 M HCl in dioxane (73 μL). The mixture was heated at 90°C for 18 h, then cooled to rt and concentrated under reduced pressure to an orange oil. The residue was purified by flash chromatography on silica gel,

eluting with 2:1 hexanes/ethyl acetate followed by methanol to provide the title compound as a dark oil (0.12 g, 90%). ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.09 (d, 2 H), 7.81 (d, 2 H), 7.75-7.67 (m, 3 H), 7.46-7.40 (m, 2 H), 7.32-7.28 (m, 2 H), 4.17-4.09 (m, 1 H), 3.26-3.23 (m, 1 H), 2.24-2.16 (m, 1 H), 2.10-2.02 (m, 1 H), 1.91-1.68 (m, 4 H); LC-MS *m/z* 458.4 (MH^+), retention time 2.48 minutes; TLC R_f 0.28 (2:1 hexanes / ethyl acetate).

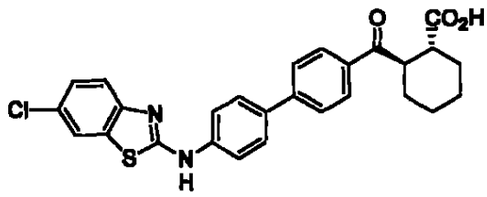
[363] (1*R*,2*R*)-2-{[4'-(1H-benzimidazol-2-ylamino)-3'-fluoro-1,1'-biphenyl-4-yl]carbonyl}-cyclopentanecarboxylic acid.



[364] Step 2. Methyl (1*R*,2*R*)-2-{[4'-(1H-benzimidazol-2-ylamino)-3'-fluoro-1,1'-biphenyl-4-yl]-carbonyl}cyclopentanecarboxylate (100 mg, 0.22 mmol) was dissolved in methanol and treated with an excess of 1 N aqueous sodium hydroxide solution (2.19 mL, 2.19 mmol). The solution was stirred at rt for 1 h, and then was concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate, and the aqueous layer was adjusted to pH 2 by the addition of 1 N aqueous HCl. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to provide an orange oil. The oil was suspended in THF and stirred until a precipitate formed. The precipitate was collected by filtration and washed with additional THF to provide the title compound as a yellow solid (30 mg, 31%, 80% ee). ^{1}H NMR (300 MHz, *DMSO-d_6*) δ 13.12 (br s, 1 H), 11.30 (br s, 1 H), 8.12 (d, 2 H), 7.96-7.76 (m, 5 H), 7.46-7.42 (m, 2 H), 7.30-7.26 (m, 2 H), 4.15-4.07 (m, 1 H), 3.27-3.19 (m, 1 H), 2.21-2.12 (m, 1 H), 2.05-1.96 (m, 1 H), 1.86-1.55 (m, 4 H); LC-MS *m/z* 444.4 (MH^+), retention time 2.79 minutes.

[365] **Example 30**

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

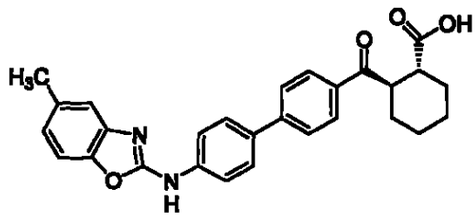


[366] To a solution of *cis*-methyl 2-[(4'-amino-1,1'-biphenyl-4-yl)carbonyl]cyclohexanecarboxylate (200 mg, 0.59 mmol) in n-butanol (8 mL) was added 2,6-dichloro-1,3-benzothiazole (241 mg,

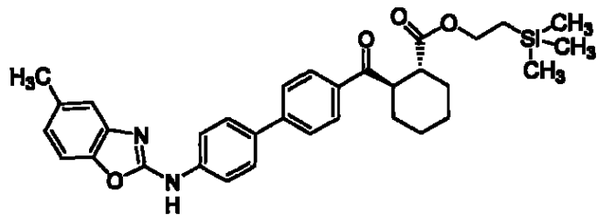
1.19 mmol), and the resulting reaction mixture was heated at 90°C overnight. The mixture was evaporated to dryness and the residue was combined with MeOH. Then 1 N NaOH (6.0 mL, 6.0 mmol) was added to the suspension, and the reaction mixture was stirred at 50°C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was suspended in water. Concentrated aqueous HCl was added to adjust the acidity to pH 1, and the precipitate was collected by filtration, washed with water and MeOH, and dried in a vacuum oven to give *trans*-2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclohexanecarboxylic acid (45 mg, 15%). LC-MS *m/z* 491.1 (MH^+), ret. time 3.90 min; ^1H NMR (400 MHz, DMSO-d_6) δ 1.13 (m, 1H), 1.28 ~ 1.51 (m, 3H), 1.78 (m, 1H), 1.93 (m, 1H), 2.09 (m, 1H), 2.68 (m, 1H), 3.63 (m, 1H), 7.35 (m, 1H), 7.60 (m, 1H), 7.80 (m, 4H), 7.90 (d, 1H), 7.96 (m, 1H), 8.05 (d, 2H), 10.75 (s, 1H).

[367] **Example 31**

***trans*-2-({4'-[(5-Methyl-1,3-benzoxazol-2-yl)amino]biphenyl-4-yl}carbonyl) cyclohexanecarboxylic acid**



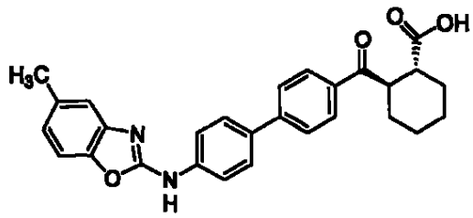
[368] *trans*-2-(Trimethylsilyl)ethyl-2-({4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]biphenyl-4-yl}-carbonyl)cyclohexanecarboxylate



[369] Step 1. *N*-(4-Bromophenyl)-5-methyl-1,3-benzoxazol-2-amine (76.70 mg, 0.25 mmol) and *trans*-2-(trimethylsilyl)ethyl-2-(4-bromobenzoyl)cyclohexanecarboxylate (105.45 mg, 0.23 mmol) were combined in a clean dry flask under argon. Toluene (25 mL), EtOH (8 mL), and saturated aqueous $NaHCO_3$ (5 mL) were added, and the resulting solution was degassed by bubbling with argon for 30 minutes. Then, [1,1'-bis(diphenylphosphino)-ferrocene]dichloro palladium(II), 1:1 complex with dichloromethane (18.78 mg, 0.02 mmol) was added, and the resulting mixture was heated at 90°C for 16 h. The reaction mixture was then diluted with EtOAc and passed through a Celite® pad, and the solvent was removed by rotary evaporation. Silica gel chromatography (Biotage cartridge), eluting with 25% EtOAc in hexane gave *trans*-2-(trimethylsilyl)ethyl-2-({4'-[(5-methyl-1,3-

benzoxazol-2-yl)amino]biphenyl-4-yl}carbonyl)cyclohexanecarboxylate (64 mg, 50%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ –0.013 (s, 9H), 0.88 (m, 2H), 1.41 (m, 3H), 1.71 ~ 2.15 (m, 5H), 2.44 (s, 3H), 2.73 (m, 1H), 3.88 (m, 1H), 4.08 (m, 2H), 7.08 (d, 1H), 7.21 (s, 1H), 7.33 (d, 1H), 7.67 (m, 2H), 7.69 (m, 2H), 7.73 (m, 2H), 7.89 (m, 1H), 7.91 (m, 1H).

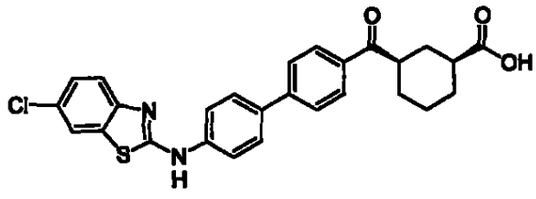
[370] *trans*-2-({4'-[(5-Methyl-1,3-benzoxazol-2-yl)amino]biphenyl-4-yl}carbonyl)cyclohexane-carboxylic acid.



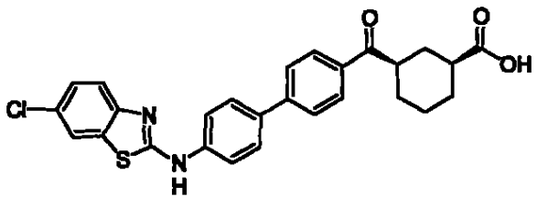
[371] Step 2. To a solution of *trans*-2-(trimethylsilyl)ethyl-2-({4'-[(5-methyl-1,3-benzoxazol-2-yl)-amino]biphenyl-4-yl}carbonyl)cyclohexanecarboxylate (64 mg, 0.12mmol) in THF (2 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 0.70 mL), and then the reaction mixture was stirred at rt for 16 h. Saturated aqueous NH_4Cl was added, and the reaction mixture was diluted with EtOAc and water. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was treated with MeOH, and the precipitate was collected by filtration and dried in a vacuum oven to give *trans*-2-({4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]biphenyl-4-yl}carbonyl)cyclohexanecarboxylic acid (44.3 mg, 84%). LC-MS *m/z* 455.3 (MH^+), ret. time 3.57 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (m, 1H), 1.37 (m, 2H), 1.63 (m, 1H), 1.85 (m, 3H), 2.05 (m, 1H), 2.38 (s, 3H), 2.69 (m, 1H), 3.95 (m, 1H), 7.03 (d, 1H), 7.33 (d, 2H), 7.76 (m, 4H), 7.85 (d, 2H), 7.93 (d, 2H), 10.73 (s, 1H).

[372] Example 32

cis-3-[4'-(6-Chloro-benzothiazol-2-ylamino)-biphenyl-4-carbonyl]-cyclohexanecarboxylic acid



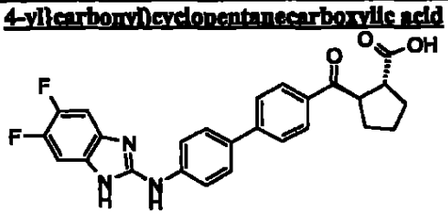
[373] *cis*-3-[4'-(6-Chloro-benzothiazol-2-ylamino)-biphenyl-4-carbonyl]-cyclohexanecarboxylic acid



[374] To a solution of 3-(4'-amino-biphenyl-4-carbonyl)-cyclohexanecarboxylic acid methyl ester (100 mg, 0.3 mmol) in butanol (5 mL), 2,6-dichloro-benzothiazole (60 mg, 0.3 mmol) and 5 drops of 4 M HCl in dioxane were added, and the reaction mixture was heated at 90°C for 5 h. An additional sample of 2,6-dichlorobenzothiazole (60 mg, 0.3 mmol) and 5 drops of 4 M HCl in dioxane were then added, and the reaction mixture was heated overnight at 90°C. The solvent was removed by rotary evaporation, the residue was dissolved in DMF (2 mL), 1 N aqueous NaOH (0.3 mL, 0.3 mmol) was added, and the mixture was heated at 75°C overnight. A solution of 1 N aqueous HCl (0.3 mL, 0.3 mmol) and methanol (5 mL) were added to the reaction mixture, and the crude product was purified by preparative reverse-phase HPLC (water/acetonitrile gradient, containing 0.1% TFA) to afford *cis*-3-[4'-(6-chloro-benzothiazol-2-ylamino)-biphenyl-4-carbonyl]-cyclohexanecarboxylic acid as a white solid (12.6 mg, yield 23.4%). ^{1}H NMR (300 MHz, DMSO) δ 8.05 (d, 2 H), 7.75-8.00 (m, 7 H), 7.50 (d, 1 H), 7.35 (d, 1 H), 3.25 (m, 1 H), 2.50 (m, 1 H), 2.20-1.90 (m, 4 H), 1.70-1.50 (m, 4 H); *LC-MS* ret. time 3.99 min (method 2), *m/z* 491.11 (MH^+).

[375] **Example 33**

***trans*-2-({4'-[(5,6-difluoro-1H-benzimidazol-2-yl)amino]biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid**



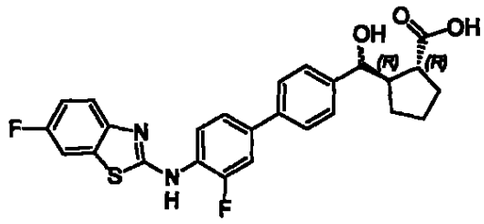
[376] Methyl 2-[(4'-aminobiphenyl-4-yl)carbonyl]cyclopentanecarboxylate (264 mg, 0.02 mmol) was dissolved in n-butanol (8 mL), 2-chloro-5,6-difluoro-1H-benzimidazole (185 mg, 0.98 mmol) and 4 N HCl (0.2 mL) were then added, and the resulting mixture was heated at 90°C for 5 h. The mixture was then cooled to rt, and solvent was removed under reduced pressure. The residue was dissolved in methanol (5 mL) and tetrahydrofuran (5 mL), and then treated with 1 N aqueous sodium hydroxide (2.45 mL, 2.45 mmol). The mixture was stirred at rt for 16 h and then concentrated under reduced pressure. The residue was purified by preparative reverse-phase HPLC (water/acetonitrile gradient, containing 0.1% TFA) to afford *trans*-2-({4'-[(5,6-difluoro-1H-benzimidazol-2-yl)amino]biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid (9.1 mg, 3 %). *LC-MS* *m/z* 462.3 (MH^+), ret. time 3.23 min;

H NMR (300 MHz, DMSO-d_6) δ 1.69- 1.81 (m, 4H), 1.98-2.18 (m, 2H), 3.14-3.22 (m, 1H), 4.04-4.09 (m, 1H), 7.38 (t, 2H), 7.77-7.84 (m, 6H), 8.05 (d, 2H).

Preparation of Compounds of Formula (Ia)

[377] **Example 34**

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



[378] To a solution of (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}carbonyl)cyclopentanecarboxylic acid (300 mg, 0.63 mmol) in THF (6 mL), a solution of sodium borohydride (23.82 mg, 0.63 mmol) in water (3 mL) was added. The reaction mixture was stirred at rt for 3 hours. The solvent was removed, the residue was then dissolved in methanol (2 mL), and the desired product was isolated by preparative reverse-phase HPLC (water/acetonitrile gradient, containing 0.1% TFA). Two diastereomers of (1*R*,2*R*)-2-[{3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}(hydroxy)methyl]cyclopentanecarboxylic acid were obtained: a more polar isomer (15 mg, yield 5%). LC-MS *m/z* 481.3 (MH^+), ret. time 3.33 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.60 (t, 1 H), 7.60 (d, 1 H), 7.50 (m, 5 H), 7.35 (d, 2 H), 7.15 (t, 1 H), 4.60 (d, 1 H), 2.65 (m, 1 H), 2.45 (m, 1 H), 1.85 (m, 1 H), 1.70-1.40 (m, 5 H); and a less polar isomer (10 mg, yield 3%); LC-MS *m/z* 481.3 (MH^+), ret. time 3.46 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.60 (t, 1 H), 7.60 (d, 1 H), 7.50 (m, 5 H), 7.35 (d, 2 H), 7.15 (t, 1 H), 4.60 (d, 1 H), 2.65 (m, 1 H), 2.45 (m, 1 H), 1.85 (m, 1 H), 1.65 (m, 1 H), 1.50 (m, 3 H), 1.25 (m, 1 H).

Preparation of Compounds of Formula (Ib)

[379] It will be recognized by those skilled in the art that compounds of Formula (Ia) can be converted to and isolated as the corresponding cyclic ester (lactone) having Formula (Ib), for example by spontaneous dehydration of the compound of Formula (Ia), or by dehydration of the compound of Formula (Ib) induced by methods known in the art. For example, such methods for the formation of compounds of Formula (Ib) from compounds of Formula (Ia) include heating under dry conditions such as in a vacuum oven; treatment with a catalytic amount of acid such as acetic acid, 4-toluenesulfonic acid, or trifluoroacetic acid in a suitable solvent such as acetonitrile, methylene chloride, or toluene; and treatment with a dehydrating reagent such as dicyclohexylcarbodiimide in the presence of 4-dimethylaminopyridine in a suitable solvent such as acetonitrile, methylene chloride, or toluene.

[380] Using appropriate starting materials and the experimental procedures described above, compounds of Formula (I) were prepared as listed in Table 1. Additional compounds of Formula (Ia) can be prepared by using appropriate starting materials and experimental procedures similar to that described above for (1*R*,2*R*)-2-[{3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}(hydroxy)methyl]cyclopentanecarboxylic acid. Compounds of Formula (Ib) can be prepared by using appropriate compounds of Formula (Ia) as starting materials and applying methods such as described above. Additional compounds of Formula (I), Formula (Ia), and Formula (Ib) such as the compounds listed in Table 2, can be prepared by the methods described herein. It will be understood by those skilled in the art that some minor modifications to the described procedures may have been made, but such modifications do not significantly affect the results of the preparation. LC-MS characterization of compounds, as listed in the table, was carried out by using the instrumentation and methods set forth above.

[381] By using the above described methods and by substituting the appropriate starting material(s), other compounds of the invention were made and characterized. These compounds, together with Examples 1-34, are summarized in Table 1 below.

Table 1

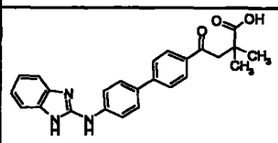
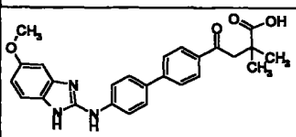
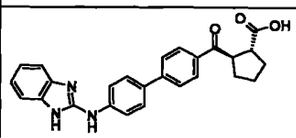
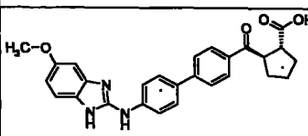
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
1		4-[4'-(1H-benzimidazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid	414.3	2.27	1	B	not chiral		2
2		4-[4'-[(5-methoxy-1H-benzimidazol-2-yl)amino]-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid	444.4	2.37	1	B	not chiral		
3		2-[[4'-(1H-benzimidazol-2-ylamino)-1,1'-biphenyl-4-yl]carbonyl]cyclopentane-carboxylic acid	426.4	2.82	1	B	trans racemic mixture		
4		2-({4'-[(5-methoxy-1H-benzimidazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	456.3	2.31	1	B	trans racemic mixture		

Table 1

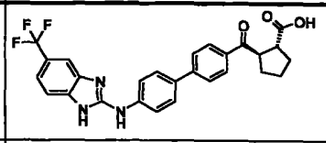
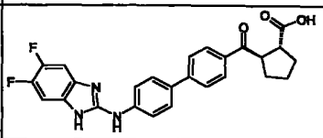
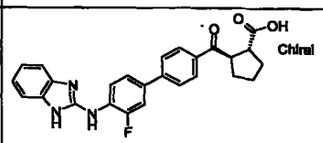
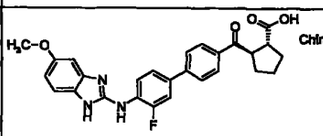
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
5		2-[(4'-[[5-(trifluoromethyl)-1H-benzimidazol-2-yl]amino]-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid	494.3	2.56	1	A	trans racemic *mixture*		
6		2-({4'-[(5,6-difluoro-1H-benzimidazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	462.3	3.23	1	B	trans racemic mixture		33
7	 Chiral	(1R,2R)-2-[(4'-(1H-benzimidazol-2-ylamino)-3'-fluoro-1,1'-biphenyl-4-yl]carbonyl]cyclopentane-carboxylic acid	444.4	2.80	1	B	R,R-trans (from chiral inter-mediate)	80	29
8	 Chiral	(1R,2R)-2-({3'-fluoro-4'-[(5-methoxy-1H-benzimidazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	474.3	2.29	1	B	R,R-trans (from chiral inter-mediate)	74	

Table 1

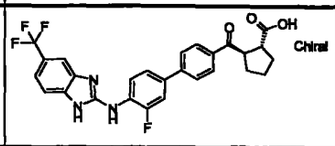
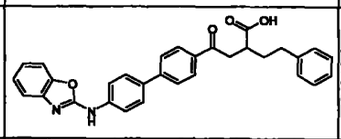
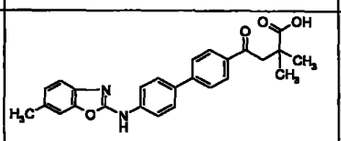
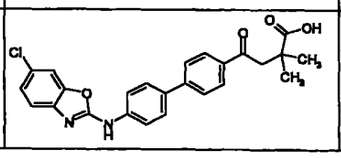
Entry No.	Structure	IUPAC name	LC-MS *m/z* . (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
9	 Chiral	(1R,2R)-2-[(3'-fluoro-4'-[[5-(trifluoromethyl)-1H-benzimidazol-2-yl]amino]-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid	512.3	2.69	1	A	R,R-trans (from chiral inter-mediate)	76	
10		4-[4'-(1,3-benzoxazol-2-ylamino)-1,1'-biphenyl-4-yl]-4-oxo-2-(2-phenylethyl)butanoic acid	461.2	3.68	1	B	racemic mixture		11
11		2,2-dimethyl-4-[4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl]-4-oxobutanoic acid	429.2	3.51	2	B	not chiral		12
12		4-[4'-[(6-chloro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid	449.1	3.99	2	B	not chiral		

Table 1

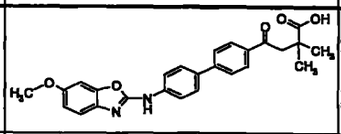
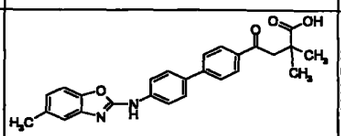
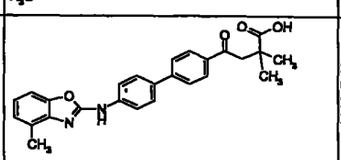
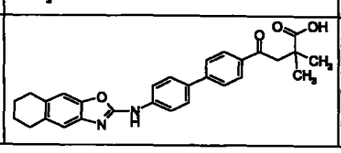
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
13		4-[4'-[(6-methoxy-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid	445.2	3.47	2	B	not chiral		
14		2,2-dimethyl-4-[4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl]-4-oxobutanoic acid	429.2	3.77	2	B	not chiral		
15		2,2-dimethyl-4-[4'-[(4-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl]-4-oxobutanoic acid	433.2	3.80	2	B	not chiral		13
16		2,2-dimethyl-4-oxo-4-[4'-(5,6,7,8-tetrahydronaphtho[2,3-d][1,3]oxazol-2-ylamino)-1,1'-biphenyl-4-yl]butanoic acid	469.2	3.99	2	B	not chiral		

Table 1

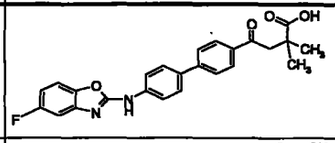
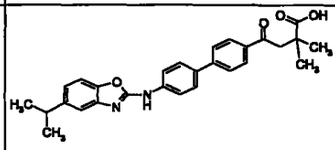
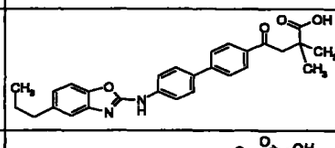
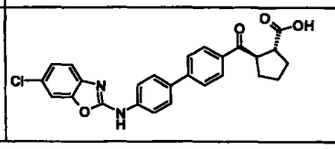
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
17		4-{4'-[(5-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid	433.2	3.80	2	B	not chiral		
18		4-{4'-[(5-isopropyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid	457.2	3.88	2	B	not chiral		
19		2,2-dimethyl-4-oxo-4-{4'-[(5-propyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}butanoic acid	457.2	3.95	2	B	not chiral		
20		2-({4'-[(6-chloro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	461.1	3.84	2	B	trans racemic mixture		

Table 1

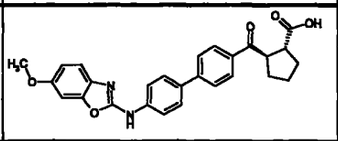
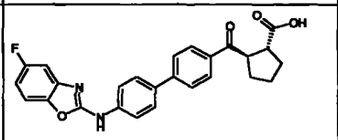
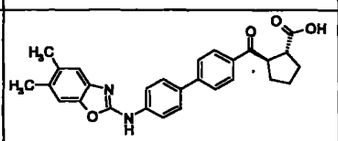
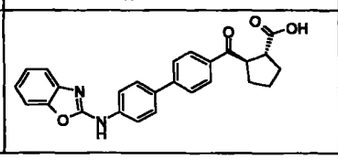
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
21		2-({4'-[(6-methoxy-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	457.2	3.55	2	B	trans racemic mixture		
22		2-({4'-[(5-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	445.2	3.66	2	B	trans racemic mixture		14
23		2-({4'-[(5,6-dimethyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	455.4	3.58	1	B	trans racemic mixture		
24		2-[[4'-(1,3-benzoxazol-2-ylamino)-1,1'-biphenyl-4-yl]carbonyl]cyclopentane-carboxylic acid	427.3	3.31	1	B	trans racemic mixture		

Table 1

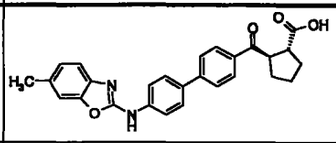
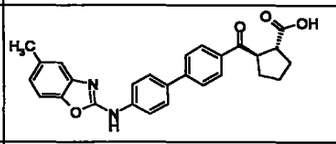
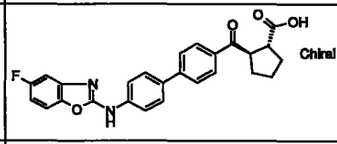
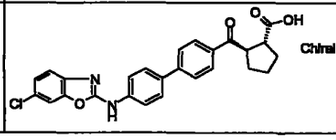
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
25		2-({4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	441.2	3.88	2	B	trans racemic mixture		
26		2-({4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	441.2	3.84	2	B	trans racemic mixture		
27	 Chiral	(1R,2R)-2-({4'-[(5-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	445.3	3.41	1	B	R,R-trans (from chiral inter-mediate)	94	
28	 Chiral	(1R,2R)-2-({4'-[(6-chloro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	461.4	3.67	1	B	R,R-trans (from chiral inter-mediate)	97	

Table 1

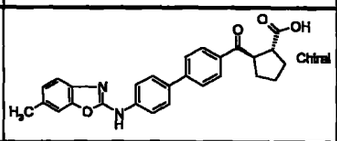
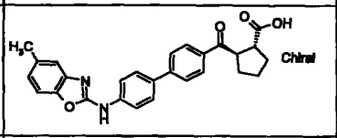
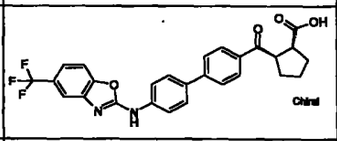
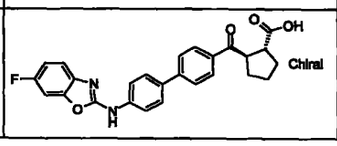
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
29	 Chiral	(1R,2R)-2-{[4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl]carbonyl}cyclopentane-carboxylic acid	441.3	3.47	1	B	R,R-trans (from chiral inter-mediate)	80	
30	 Chiral	(1R,2R)-2-{[4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl]carbonyl}cyclopentane-carboxylic acid	441.3	3.48	1	A	R,R-trans (from chiral prep-HPLC)	96	27
31	 Chiral	(1R,2R)-2-[(4'-[[5-(trifluoromethyl)-1,3-benzoxazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid	495.3	4.15	1	A	R,R-trans (from chiral inter-mediate)	98	
32	 Chiral	(1R,2R)-2-{[4'-[(6-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl]carbonyl}cyclopentane-carboxylic acid	445.2	3.39	1	B	R,R-trans (from chiral prep-HPLC)	>99	

Table 1

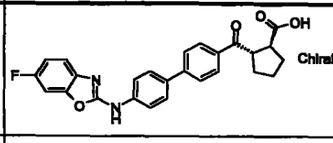
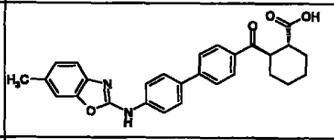
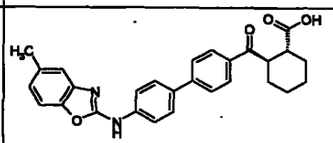
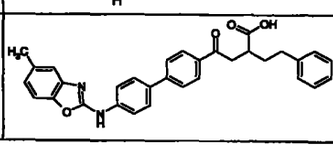
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
33		(1S,2S)-2-({4'-[(6-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	445.2	3.39	1	B	S,S-trans (from chiral prep-HPLC)	>99	
34		2-({4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclohexane-carboxylic acid	455.3	3.57	1	A	trans racemic mixture		
35		2-({4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclohexane-carboxylic acid	455.3	3.57	1	A	trans racemic mixture		31
36		4-{4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxo-2-(2-phenylethyl)butanoic acid	505.3	3.74	1	A	racemic mixture		

Table 1

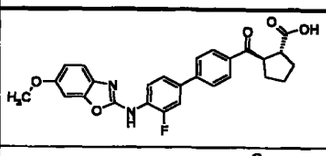
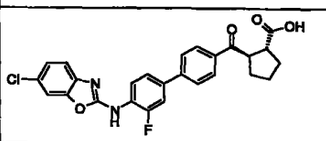
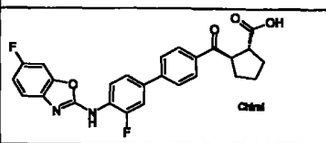
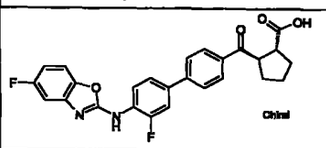
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
37		2-({3'-fluoro-4'-[(6-methoxy-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	475.2	3.29	2	B	trans racemic mixture		
38		2-({4'-[(6-chloro-1,3-benzoxazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	479.1	3.77	2	B	trans racemic mixture		
39		(1R,2R)-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	463.3	3.44	1	B	R,R-trans (from chiral prep-HPLC)	80	
40		(1R,2R)-2-({3'-fluoro-4'-[(5-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	463.3	3.42	1	B	R,R-trans (from chiral prep-HPLC)	82	

Table 1

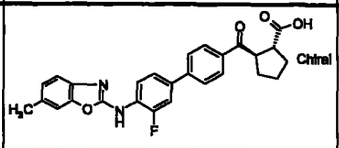
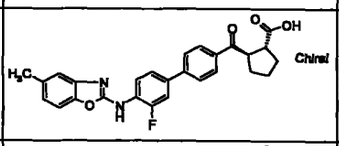
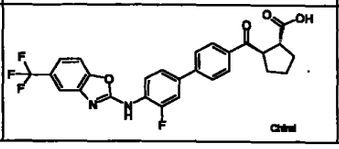
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
41	 Chiral	(1R,2R)-2-({3'-fluoro-4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	459.3	3.57	1	B	R,R-trans (from chiral inter-mediate)	80	15
42	 Chiral	(1R,2R)-2-({3'-fluoro-4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	459.3	3.54	1	A	R,R-trans (from chiral inter-mediate)	94	
43	 Chiral	(1R,2R)-2-({3'-fluoro-4'-[(5-(trifluoromethyl)-1,3-benzoxazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid	513.3	4.53	1	A	R,R-trans (from chiral inter-mediate)	96	

Table 1

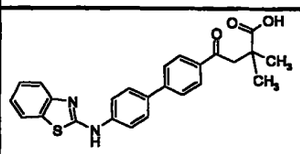
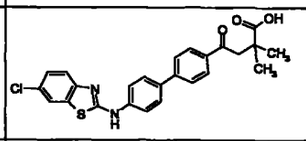
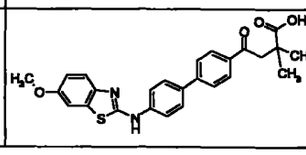
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
44		4-[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid	431.2	3.40	1	B	not chiral		1
45		4-{4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid	465.2	3.76	1	B	not chiral		
46		4-{4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid	461.2	3.40	1	B	not chiral		

Table 1

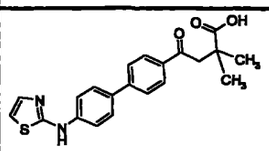
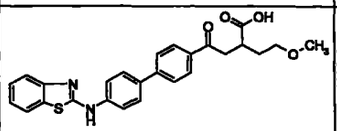
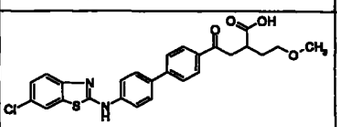
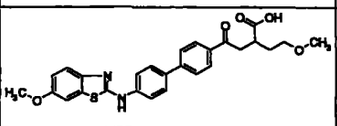
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
47		2,2-dimethyl-4-oxo-4-[4'-(1,3-thiazol-2-ylamino)-1,1'-biphenyl-4-yl]butanoic acid	381.4	2.53	1	B	not chiral		3
48		4-[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2-(2-methoxyethyl)-4-oxobutanoic acid	461.2	3.29	2	B	racemic mixture		6
49		4-[4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-2-(2-methoxyethyl)-4-oxobutanoic acid	495.1	3.66	.2	B	racemic mixture		
50		4-[4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-2-(2-methoxyethyl)-4-oxobutanoic acid	491.2	3.25	2	B	racemic mixture		

Table 1

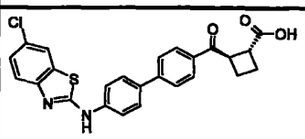
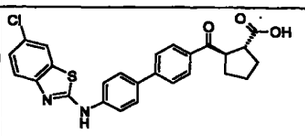
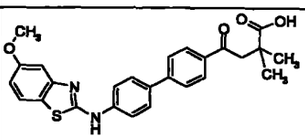
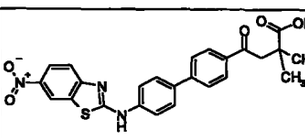
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
51		2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclobutane-carboxylic acid	463.1	3.69	1	B	trans racemic mixture		19
52		2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	477.4	3.81	1	B	trans racemic mixture		
53		4-{4'-[(5-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid	461.4	3.33	1	B	not chiral		
54		2,2-dimethyl-4-{4'-[(6-nitro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxobutanoic acid	476.2	3.49	1	B	not chiral		

Table 1

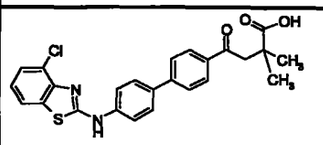
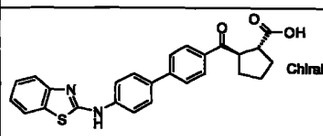
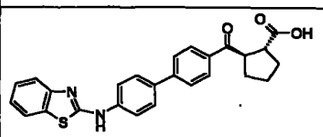
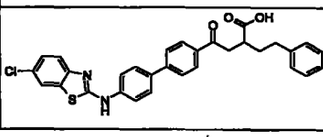
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
55		4-[4'-[(4-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid	465.4	3.82	1	B	not chiral		
56		(1R,2R)-2-[[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]carbonyl]cyclopentane-carboxylic acid	443.3	3.43	1	B	R,R-trans (from chiral inter-mediate)	97	
57		2-[[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]carbonyl]cyclopentane-carboxylic acid	443.4	3.48	1	B	trans racemic mixture		
58		4-[4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-4-oxo-2-(2-phenylethyl)butanoic acid	541.3	4.07	1	B	racemic mixture		4

Table 1

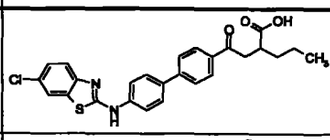
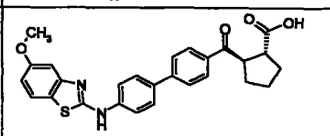
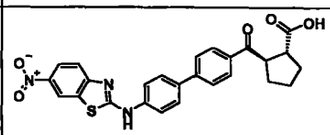
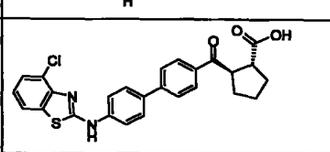
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
59		2-(2-[4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-2-oxoethyl)pentanoic acid	479.3	3.88	1	B	racemic mixture		5
60		2-({4'-[(5-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	473.3	3.42	1	B	trans racemic mixture		
61		2-({4'-[(6-nitro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	488.2	3.59	1	B	trans racemic mixture		
62		2-({4'-[(4-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	477.3	3.72	1	B	trans racemic mixture		

Table 1

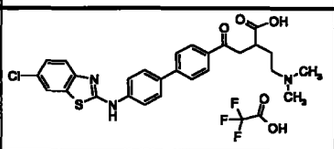
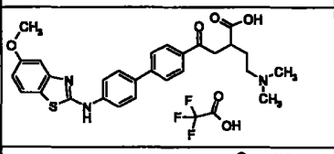
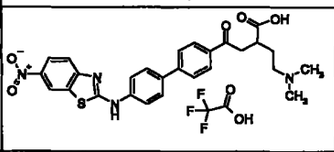
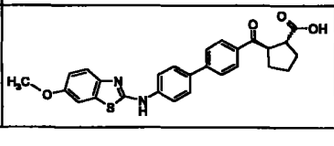
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
63		4-[4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-2-[2-(dimethylamino)ethyl]-4-oxobutanoic acid (trifluoroacetate salt)	508.1	2.66	1	B	racemic mixture		7
64		2-[2-(dimethylamino)ethyl]-4-[4'-[(5-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-4-oxobutanoic acid (trifluoroacetate salt)	504.2	2.42	1	B	racemic mixture		
65		2-[2-(dimethylamino)ethyl]-4-[4'-[(6-nitro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-4-oxobutanoic acid (trifluoroacetate salt)	519.2	2.52	1	B	racemic mixture		
66		2-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	473.3	3.41	1	B	trans racemic mixture		

Table 1

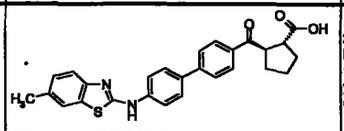
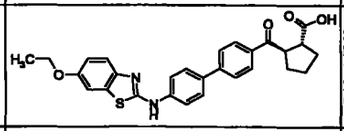
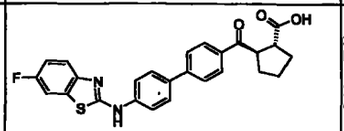
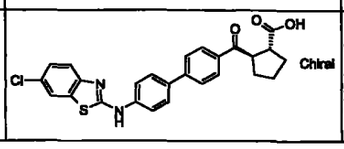
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
67		2-({4'-[(6-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	457.3	3.57	1	A	trans racemic mixture		20
68		2-({4'-[(6-ethoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	487.4	3.64	1	B	trans racemic mixture		
69		2-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	461.4	3.63	1	B	trans racemic mixture		
70		(1R,2R)-2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	477.4	3.85	1	B	R,R-trans (from chiral prep-HPLC)	99	

Table 1

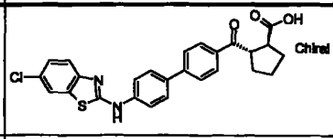
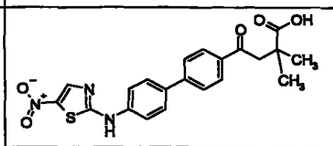
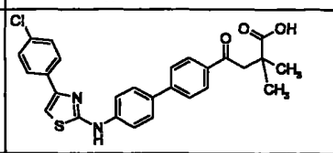
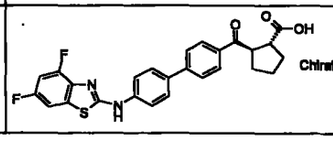
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
71		(1S,2S)-2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	477.4	3.85	1	B	S,S-trans (from chiral prep-HPLC)	92	
72		2,2-dimethyl-4-[4'-[(5-nitro-1,3-thiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-4-oxobutanoic acid	426.2	3.14	1	B	not chiral		9
73		4-(4'-[[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoic acid	491.2	3.83	1	B	not chiral		10
74		(1R,2R)-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	479.2	3.84	1	B	R,R-trans (from chiral prep-HPLC)	99	23

Table 1

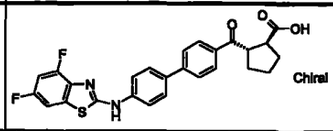
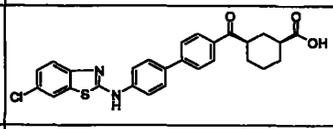
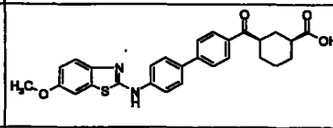
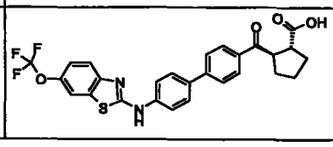
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
75	 Chiral	(1S,2S)-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	479.2	3.65	1	B	S,S-trans (from chiral prep-HPLC)	74	24
76		3-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclohexane-carboxylic acid	491.1	3.99	2	B	cis racemic mixture		32
77		3-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclohexane-carboxylic acid	487.2	3.11	2	B	cis racemic mixture		
78		2-[(4'-[(6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino)-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid	527.3	3.87	1	B	trans racemic mixture		

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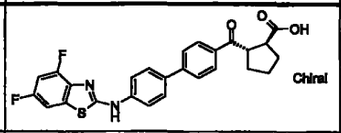
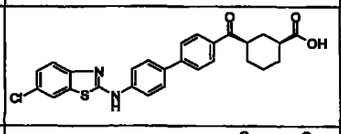
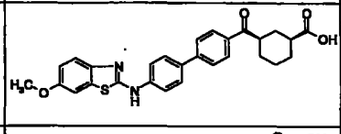
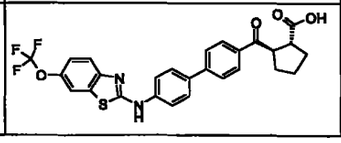
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
75		(1S,2S)-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	479.2	3.65	1	B	S,S-trans (from chiral prep-HPLC)	74	24
76		3-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclohexane-carboxylic acid	491.1	3.99	2	B	cis racemic mixture		32
77		3-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclohexane-carboxylic acid	487.2	3.11	2	B	cis racemic mixture		
78		2-({4'-[(6-(trifluoromethoxy)-1,3-benzothiazol-2-yl)amino)-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	527.3	3.87	1	B	trans racemic mixture		

Table 1

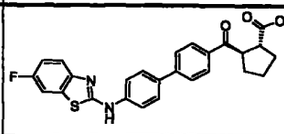
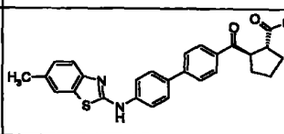
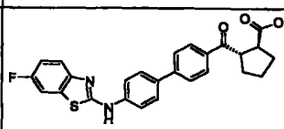
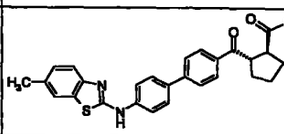
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
79	 Chiral	(1R,2R)-2-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	461.1	3.63	1	B	R,R-trans (from chiral prep-HPLC)	99	
80	 Chiral	(1R,2R)-2-({4'-[(6-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	457.4	3.57	1	B	R,R-trans (from chiral prep-HPLC)	99	
81	 Chiral	(1S,2S)-2-({4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	461.3	3.55	1	B	S,S-trans (from chiral prep-HPLC)	99	
82	 Chiral	(1S,2S)-2-({4'-[(6-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	457.4	3.57	1	B	S,S-trans (from chiral prep-HPLC)	99	

Table 1

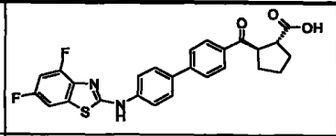
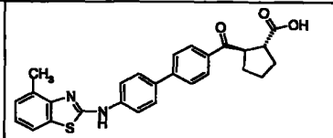
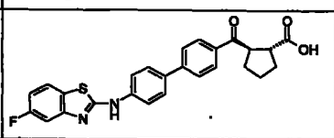
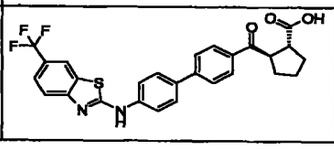
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
83		2-{(4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl)carbonyl}cyclopentane-carboxylic acid	479.3	4.12	1	B	trans racemic mixture		22
84		2-{(4'-[(4-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl)carbonyl}cyclopentane-carboxylic acid	457.3	3.71	1	B	trans racemic mixture		
85		2-{(4'-[(5-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl)carbonyl}cyclopentane-carboxylic acid	461.3	3.56	1	B	trans racemic mixture		16
86		2-{(4'-[(6-(trifluoromethyl)-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl)carbonyl}cyclopentane-carboxylic acid	511.3	4.27	1	B	trans racemic mixture		17

Table 1

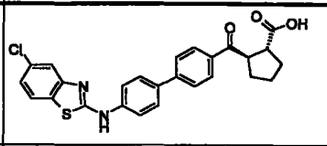
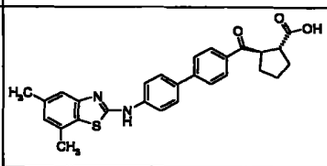
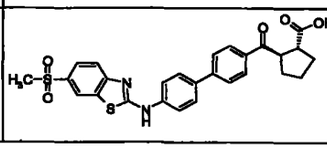
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
87		2-({4'-[(5-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	477.2	3.78	1	B	trans racemic mixture		
88		2-({4'-[(5,7-dimethyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	471.3	3.70	1	B	trans racemic mixture		
89		2-[(4'-[(6-(methylsulfonyl)-1,3-benzothiazol-2-yl)amino)-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid	521.2	3.60	1	B	trans racemic mixture		

Table 1

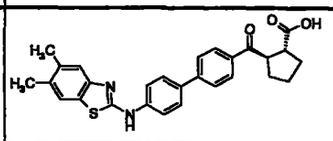
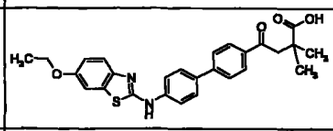
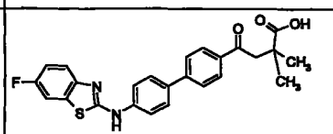
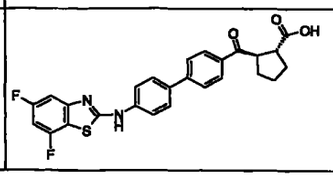
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
90		2-({4'-[(5,6-dimethyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	471.3	3.65	1	B	trans racemic mixture		
91		4-[4'-[(6-ethoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid	475.2	3.47	1	B	not chiral		
92		4-[4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid	449.2	3.46	1	B	not chiral		
93		2-({4'-[(5,7-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	479.2	3.75	1	B	trans racemic mixture		28

Table 1

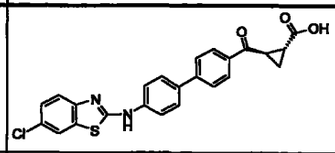
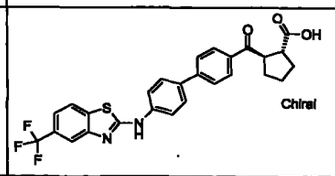
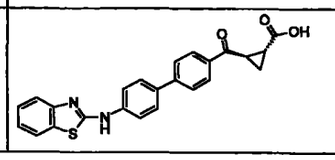
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
94		2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopropane-carboxylic acid	449.2	3.70	1	B	trans racemic mixture		
95		(1R,2R)-2-{[4'-([5-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino)-1,1'-biphenyl-4-yl]carbonyl}cyclopentane-carboxylic acid	511.1	3.82	1	A	R,R-trans (from chiral inter-mediate)	90	
96		2-{[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]carbonyl}cyclopropane-carboxylic acid	415.2	3.21	1	B	trans racemic mixture		

Table 1

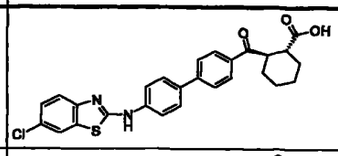
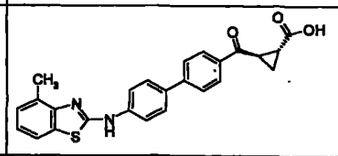
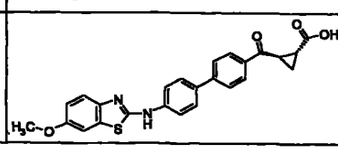
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
97		2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclohexane-carboxylic acid	491.2	3.90	1	B	trans racemic mixture		
98		2-({4'-[(4-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopropane-carboxylic acid	429.2	3.49	1	B	trans racemic mixture		
99		2-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopropane-carboxylic acid	445.2	3.17	1	B	trans racemic mixture		

Table 1

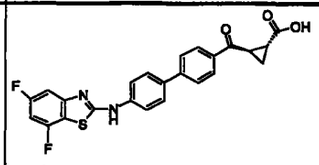
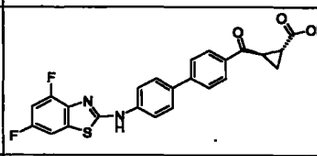
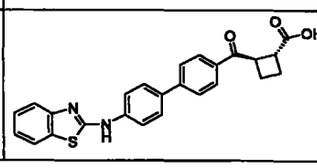
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
100		2-({4'-[(5,7-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopropane-carboxylic acid	451.1	3.53	1	B	trans racemic mixture		
101		2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopropane-carboxylic acid	451.1	3.41	1	B	trans racemic mixture		
102		2-[[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]carbonyl]cyclobutane-carboxylic acid	429.2	3.27	1	B	trans racemic mixture		

Table 1

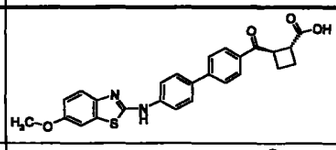
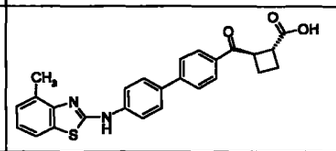
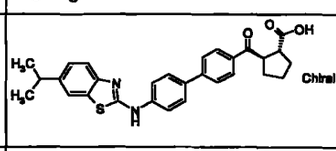
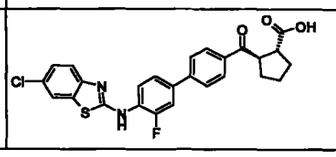
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
103		2-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclobutane-carboxylic acid	459.2	3.42	1	B	trans racemic mixture		
104		2-({4'-[(4-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclobutane-carboxylic acid	443.2	3.73	1	B	trans racemic mixture		
105	 Chiral	(1R,2R)-2-({4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	485.3	4.31	1	A	R,R-trans (from chiral inter-mediate)	90	
106		2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	495.1	3.91	2	B	trans racemic mixture		

Table 1

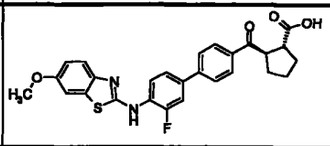
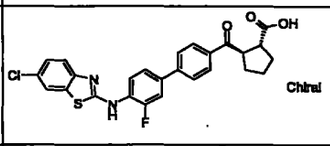
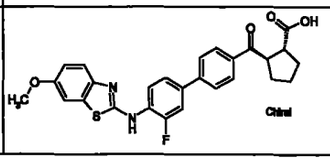
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
107		2-({3'-fluoro-4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	491.1	3.77	2	B	trans racemic mixture		
108	 Chiral	(1R,2R)-2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	495.3	4.01	1	A	R,R-trans (from chiral inter-mediate)	>99	16
109	 Chiral	(1R,2R)-2-({3'-fluoro-4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	491.3	3.56	1	B	R,R-trans (from chiral inter-mediate)	89	8

Table 1

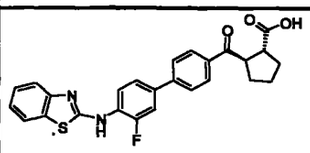
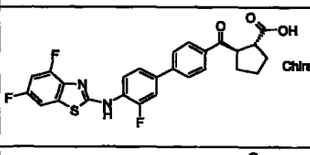
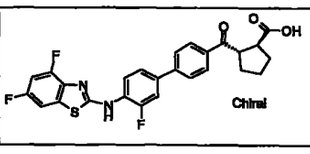
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110		2-[[4'-(1,3-benzothiazol-2-ylamino)-3'-fluoro-1,1'-biphenyl-4-yl]carbonyl]cyclopentane-carboxylic acid	461.4	3.60	1	B	trans racemic mixture		
111	 Chiral	(1R,2R)-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	497.2	3.71	1	B	R,R-trans (from chiral prep-HPLC)	>99	
112	 Chiral	(1S,2S)-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	497.2	3.71	1	B	S,S-trans (from chiral prep-HPLC)	95	

Table 1

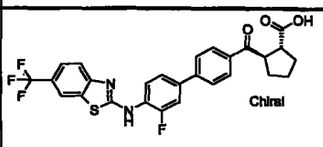
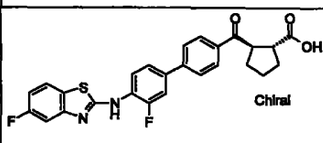
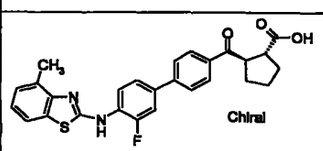
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
113	 Chiral	(1R,2R)-2-[[3'-fluoro-4'-[[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino]-1,1'-biphenyl-4-yl]carbonyl]cyclopentane-carboxylic acid	529.3	4.33	1	B	R,R-trans (from chiral inter-mediate)	97	
114	 Chiral	(1R,2R)-2-({3'-fluoro-4'-[(5-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	479.3	4.10	1	B	R,R-trans (from chiral inter-mediate)	90	
115	 Chiral	(1R,2R)-2-({3'-fluoro-4'-[(4-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	475.3	3.97	1	A	R,R-trans (from chiral inter-mediate)	83	21

Table 1

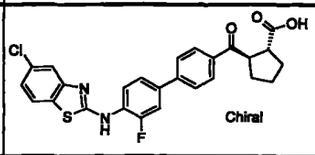
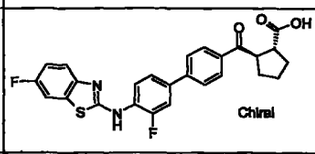
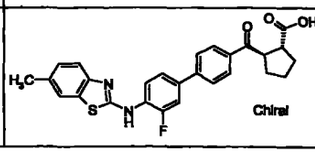
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
116	 Chiral	(1R,2R)-2-({4'-[(5-chloro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	495.2	3.85	1	B	R,R-trans (from chiral inter-mediate)	98	
117	 Chiral	(1R,2R)-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	479.3	3.84	1	A	R,R-trans (from chiral inter-mediate)	96	26
118	 Chiral	(1R,2R)-2-({3'-fluoro-4'-[(6-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	475.3	3.71	1	B	R,R-trans (from chiral prep-HPLC)	90	

Table 1

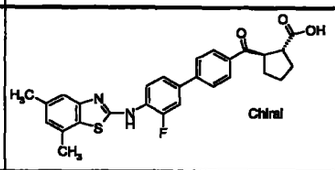
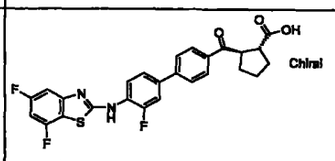
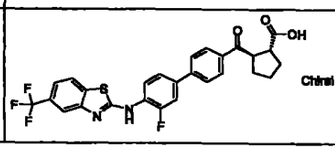
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
119	 Chiral	(1R,2R)-2-({4'-[(5,7-dimethyl-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	489.3	3.85	1	A	R,R-trans (from chiral intermediate)	66	
120	 Chiral	(1R,2R)-2-({4'-[(5,7-difluoro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	497.2	3.84	1	A	R,R-trans (from chiral intermediate)	80	
121	 Chiral	(1R,2R)-2-[(3'-fluoro-4'-{[5-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid	529.1	3.90	1	A	R,R-trans (from chiral intermediate)	90	

Table 1

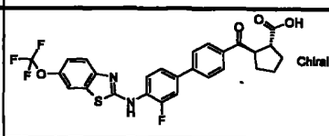
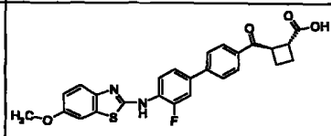
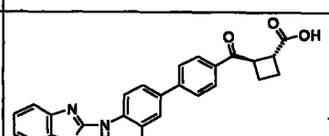
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS *method*	synthetic route	chirality & route	% ee	Example No. described in text
122	 Chiral	(1R,2R)-2-[(3'-fluoro-4'-[[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid	545.3	3.93	1	A	R,R-trans (from chiral inter-mediate)	95	25
123		2-({3'-fluoro-4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclobutane-carboxylic acid	477.2	3.54	1	A	trans racemic mixture		
124		2-[(4'-(1,3-benzothiazol-2-ylamino)-3'-fluoro-1,1'-biphenyl-4-yl]carbonyl)cyclobutane-carboxylic acid	447.1	3.56	1	A	trans racemic mixture		

Table 1

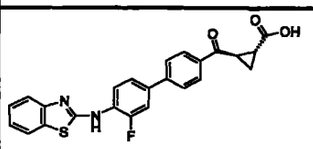
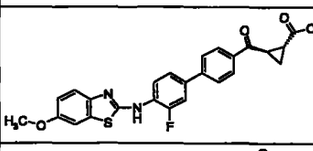
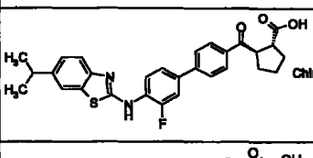
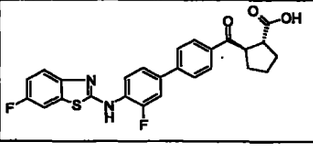
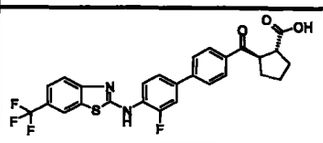
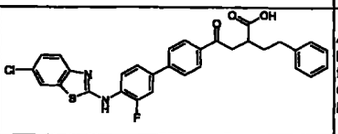
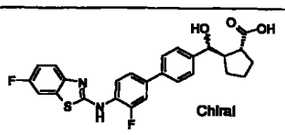
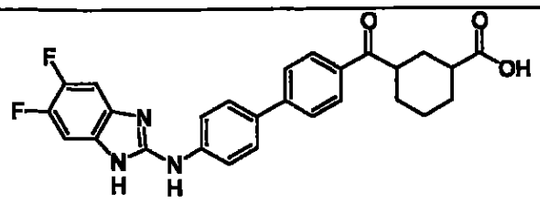
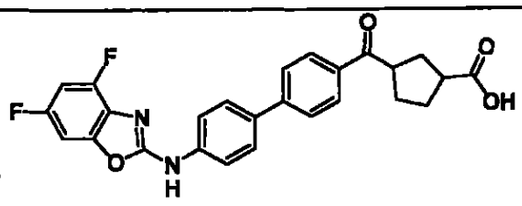
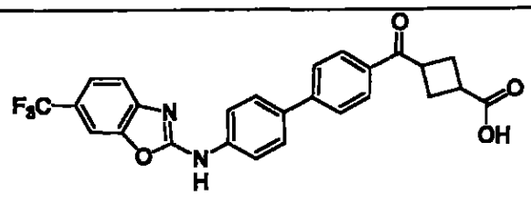
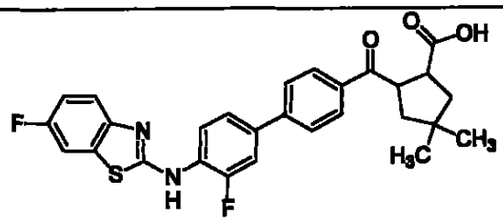
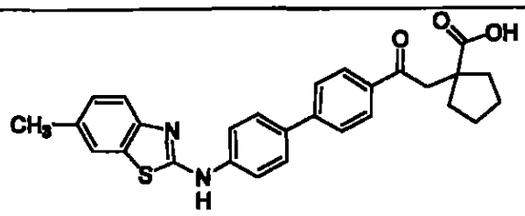
Entry No.	Structure	IUPAC name	LC-MS *m/z* (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
125		2-[[4'-(1,3-benzothiazol-2-ylamino)-3'-fluoro-1,1'-biphenyl-4-yl]carbonyl]cyclopropane-carboxylic acid	433.2	3.31	1	A	trans racemic mixture		
126		2-({3'-fluoro-4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopropane-carboxylic acid	463.2	3.47	1	A	trans racemic mixture		
127	 Chiral	(1R,2R)-2-({3'-fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	503.3	4.46	1	A	R,R-trans (from chiral inter-mediate)	90	
128		2-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid	479.3	3.65	1	B	trans racemic mixture		

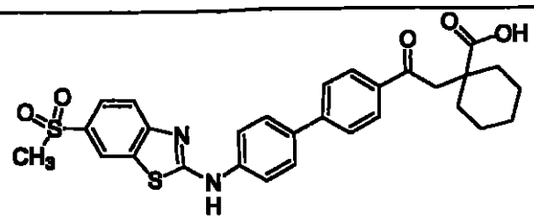
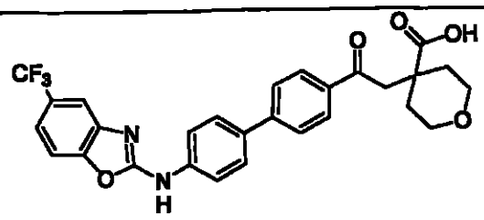
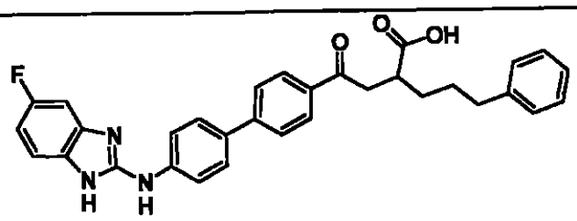
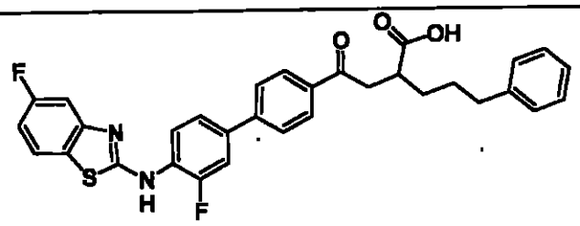
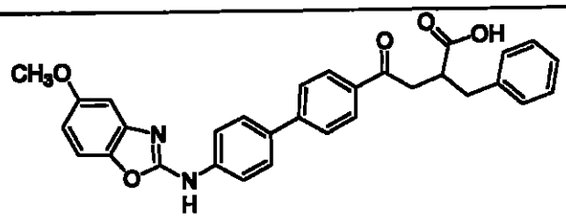
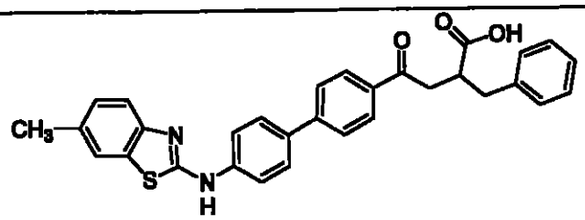
Table 1

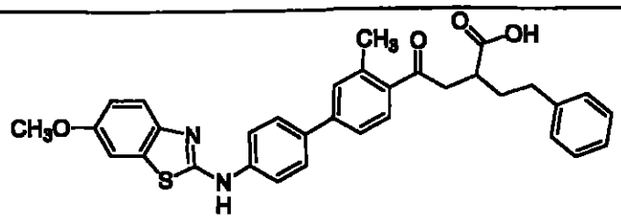
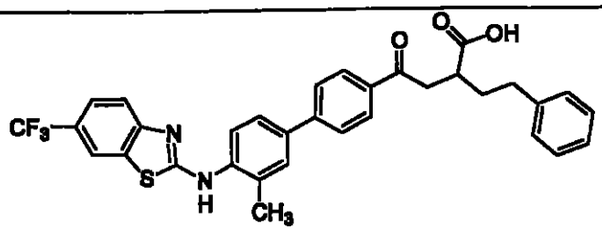
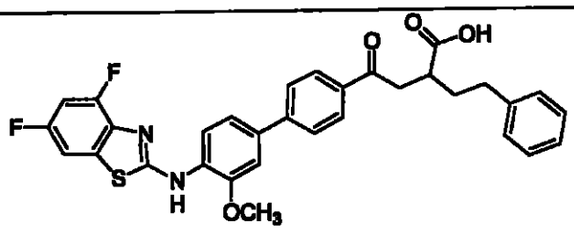
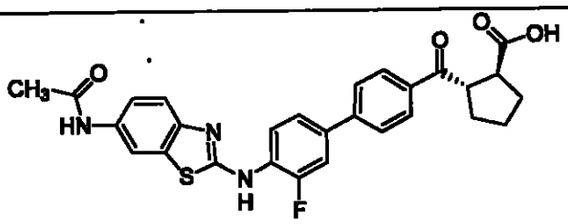
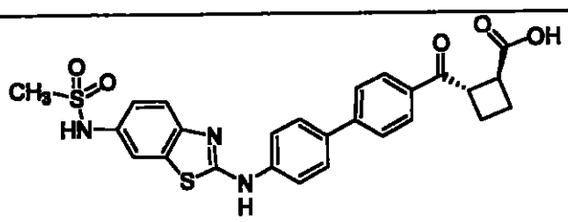
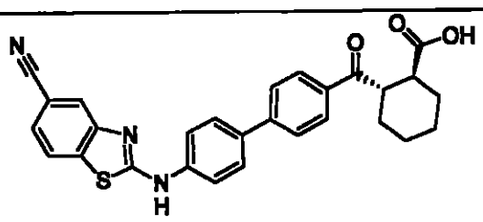
Entry No.	Structure	IUPAC name	LC-MS m/z (MH+)	LC-MS ret. time (min)	LC-MS method	synthetic route	chirality & route	% ee	Example No. described in text
129		2-[(3'-fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid	529.3	3.89	1	A	trans racemic mixture		
130		4-[4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl]-4-oxo-2-(2-phenylethyl)butanoic acid	559.2	4.13	1	A	racemic mixture		
131	 Chiral	(1R,2R)-2-[(3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-biphenyl-4-yl)(hydroxy)-methyl]-cyclopentane-carboxylic acid	481.3	two isomers: 3.33 & 3.46	1	N/A	R,R-trans-cyclo-pentyl (from chiral inter-mediate)		34

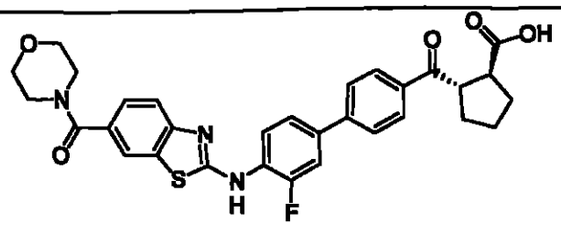
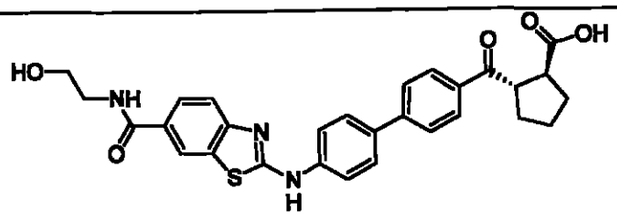
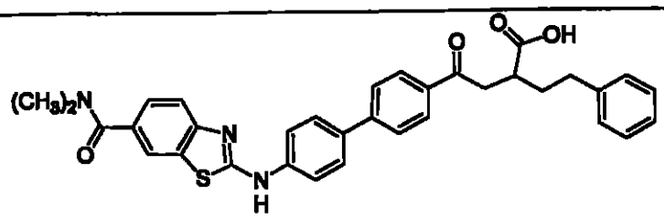
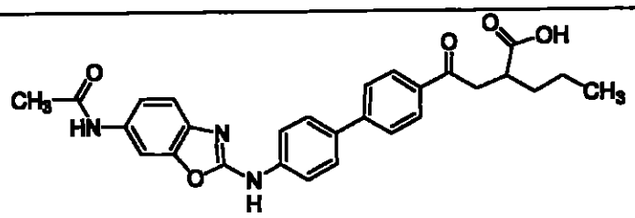
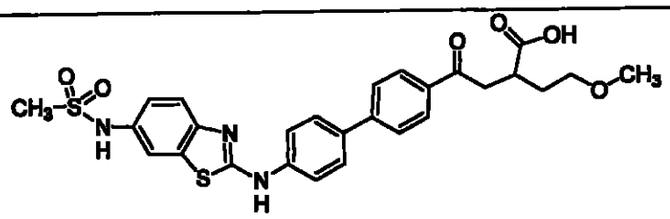
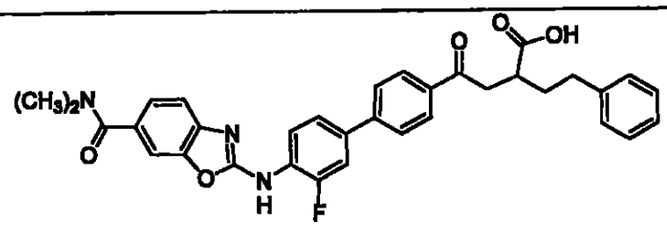
[382] By using the methods described above and by selecting the appropriate starting materials, other compounds of the invention can be made and are illustrated in Table 2 below.

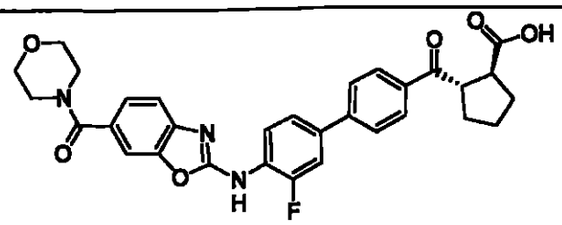
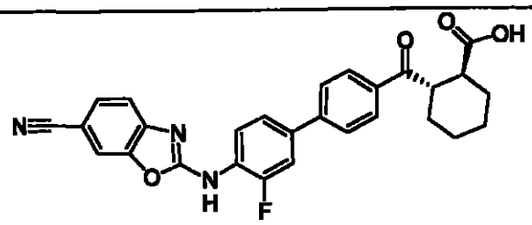
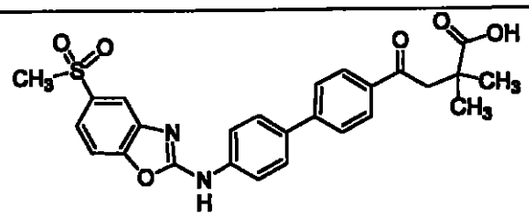
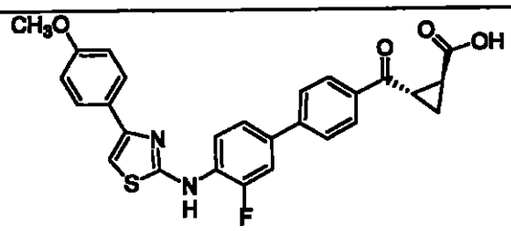
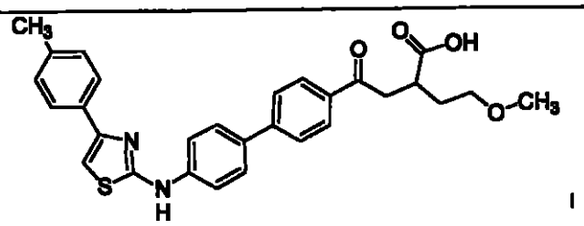
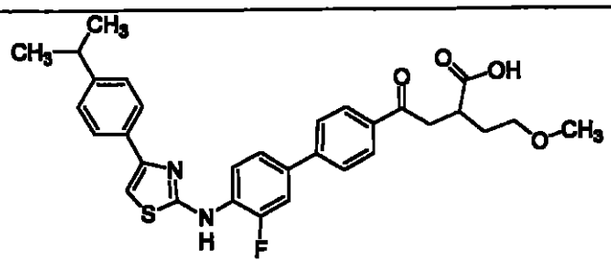
Table 2

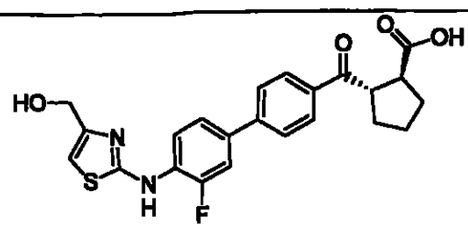
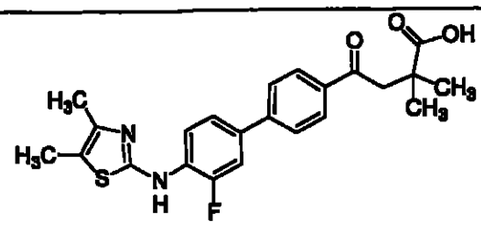
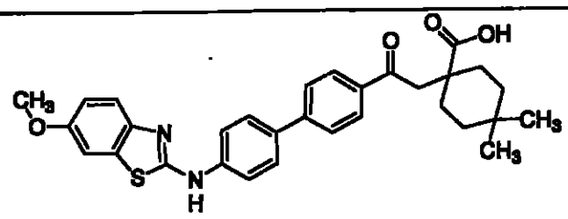
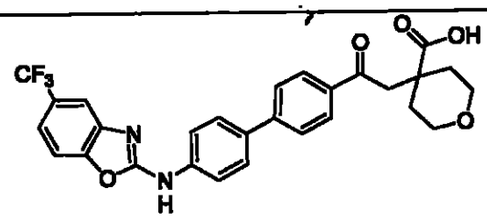
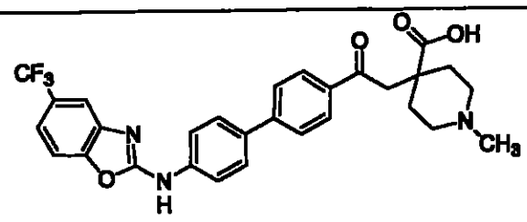
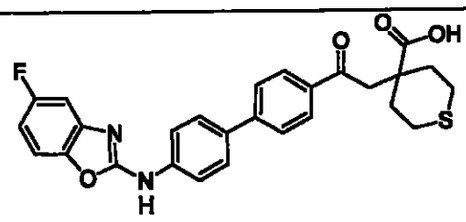
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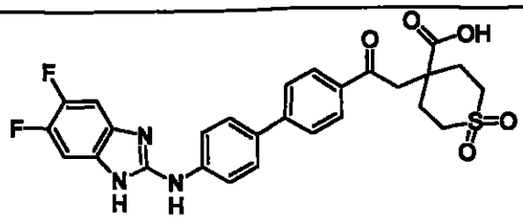
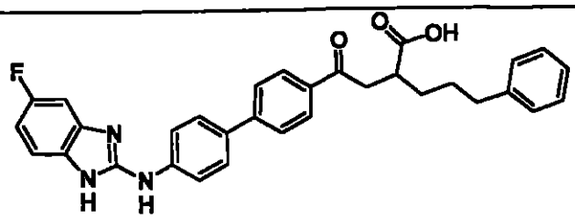
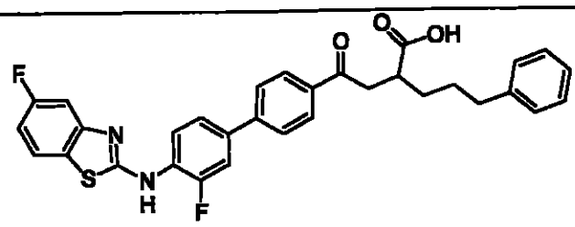
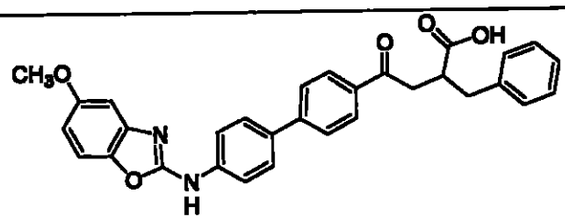
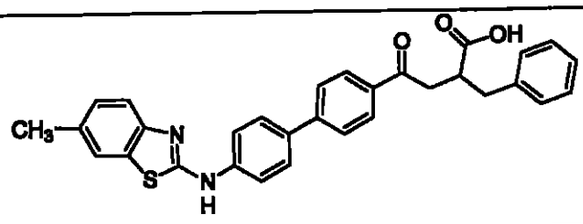
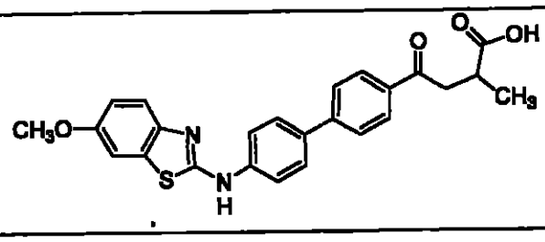
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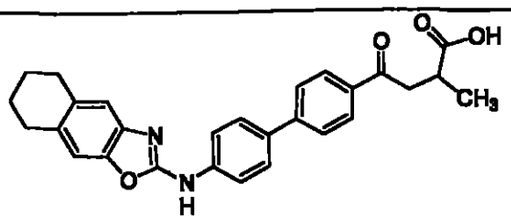
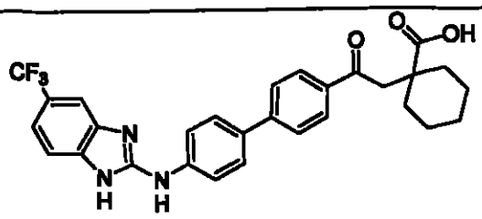
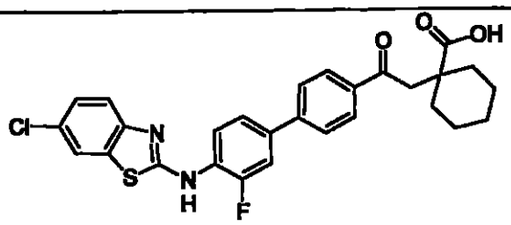
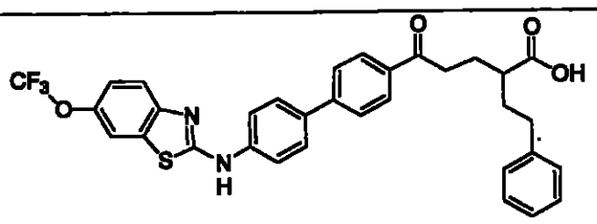
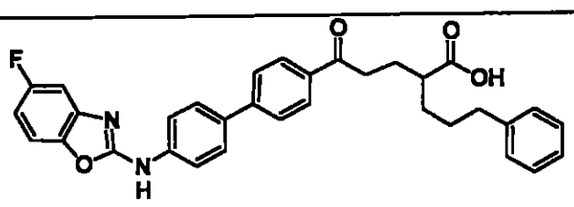
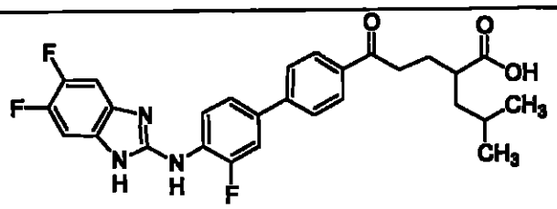
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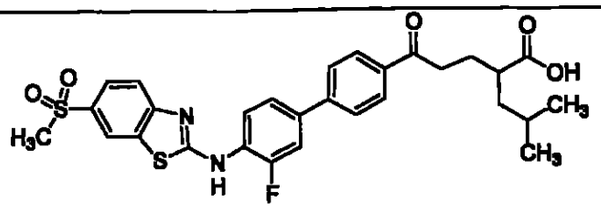
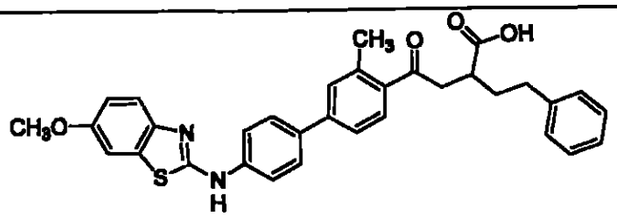
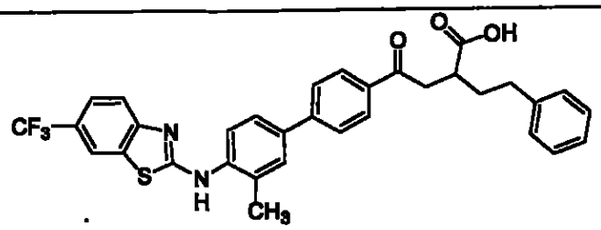
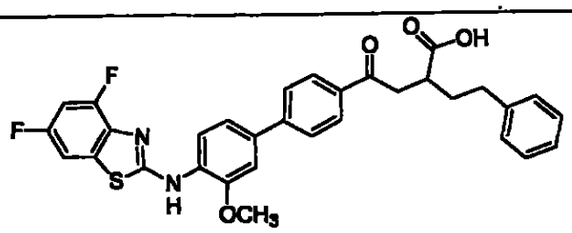
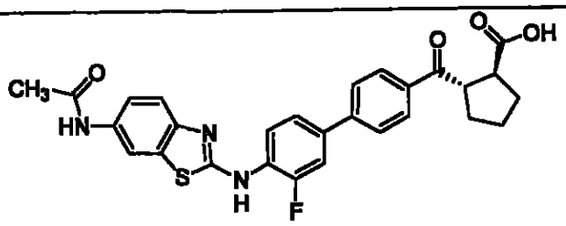
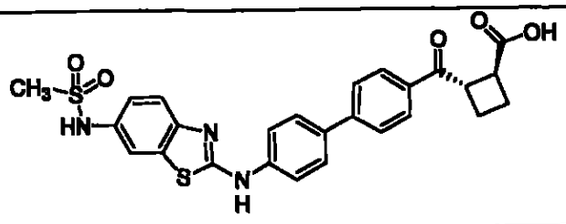
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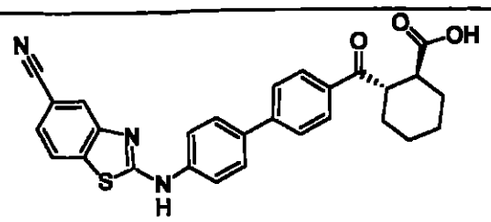
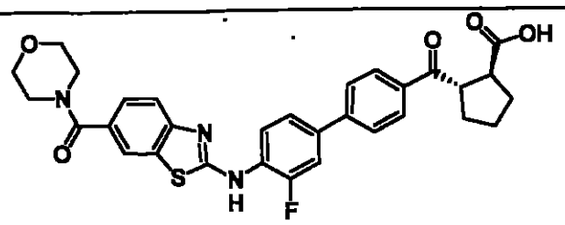
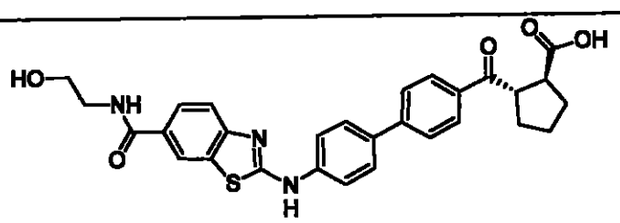
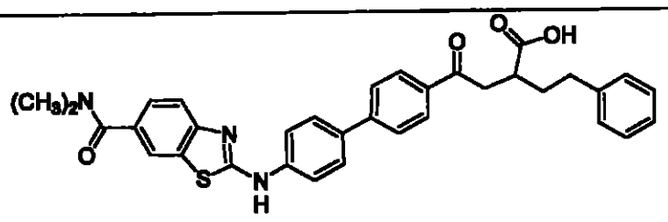
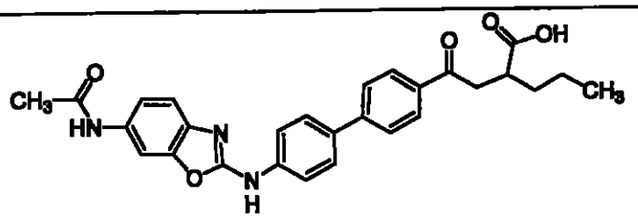
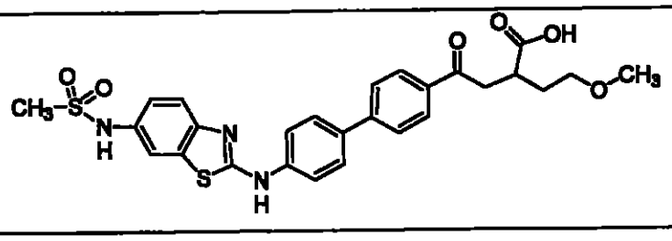
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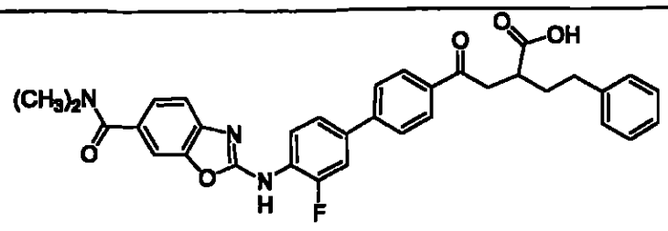
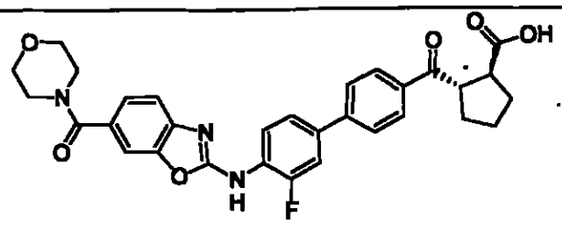
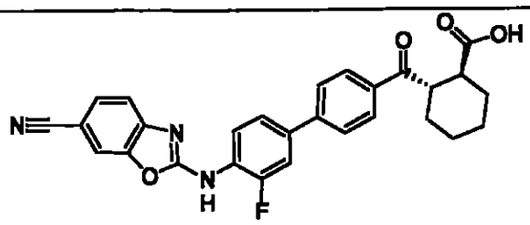
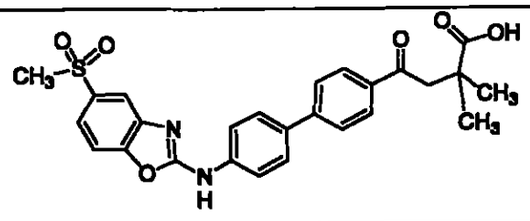
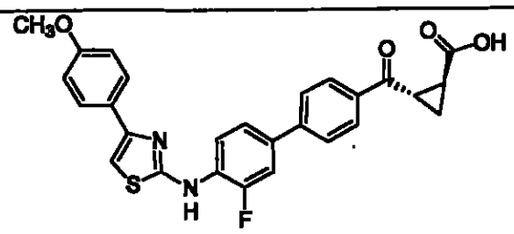
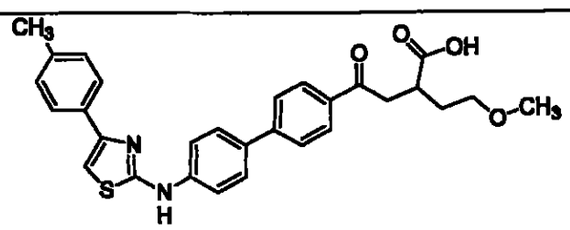
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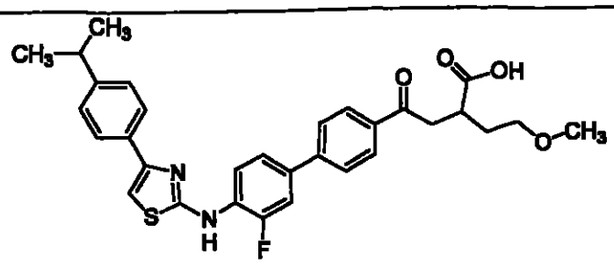
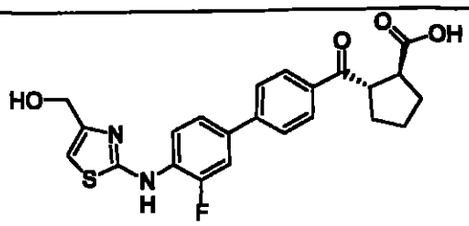
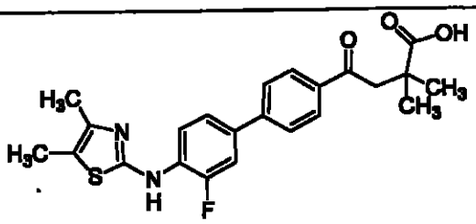
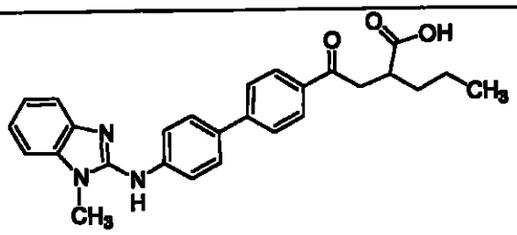
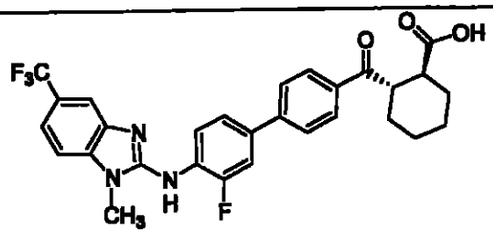
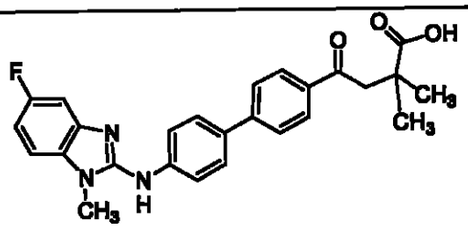
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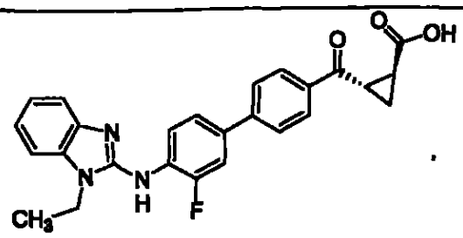
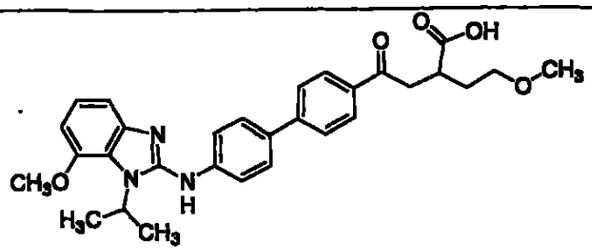
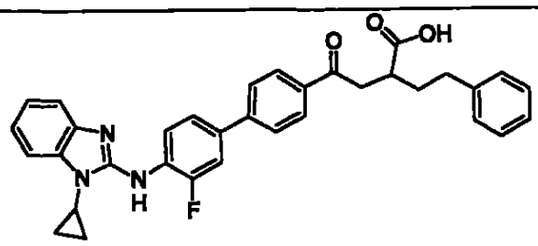
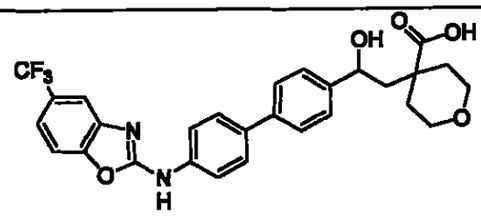
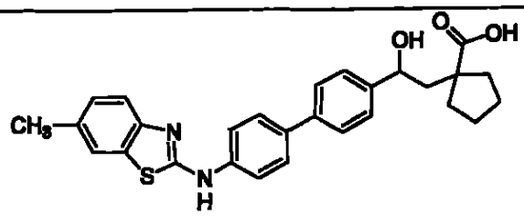
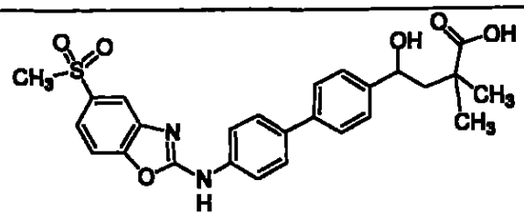
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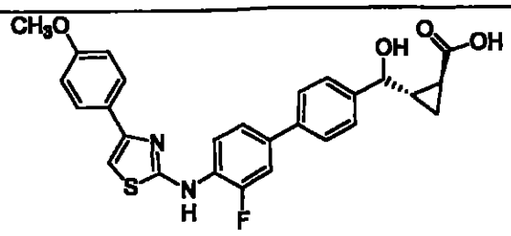
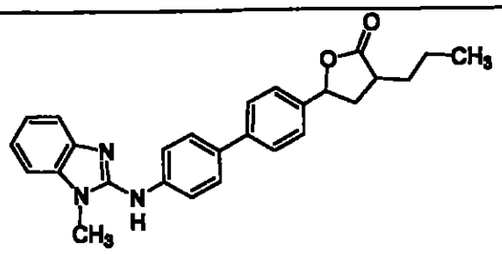
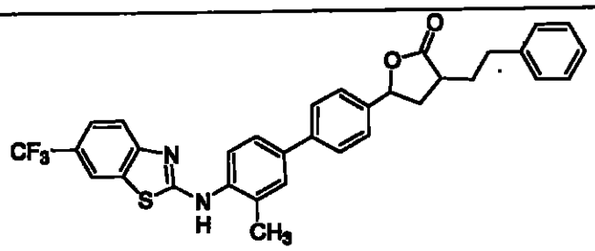
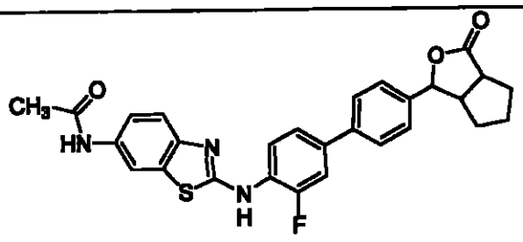
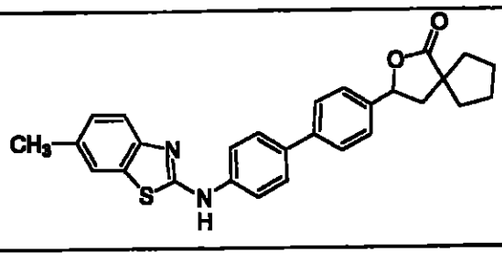
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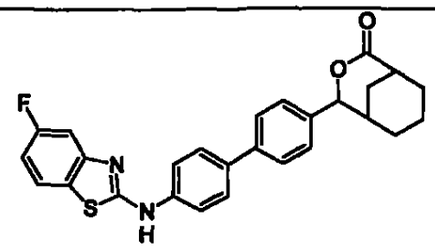
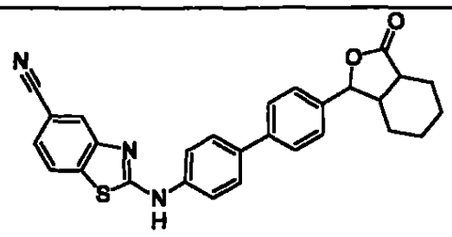
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Entry No.	Structure
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Methods of Use

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

[384] 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.

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

[386] 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.

[387] The term "combination therapy" or "co-therapy" means the administration of two or more therapeutic agents to treat an obese 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.

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

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

[390] The compounds of Formula (I) , Formula (Ia), and Formula (Ib) 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) , Formula (Ia), or Formula (Ib) that is effective in treating the target condition.

[391] 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.

[392] 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.

[393] Compounds of Formula (I) , Formula (Ia), or Formula (Ib) 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) , Formula (Ia), or Formula (Ib) and one or more additional therapeutic agents, as well as administration of the compound of Formula (I) , Formula (Ia), or Formula (Ib) and each additional therapeutic agents in its own separate pharmaceutical dosage formulation. For example, a compound of Formula (I) , Formula (Ia), or Formula (Ib) 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.

[394] Where separate dosage formulations are used, the compound of Formula (I) , Formula (Ia), or Formula (Ib) 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).

[395] For example, the compounds of Formula (I) , Formula (Ia), or Formula (Ib) may be used in combination with other therapies and drugs useful for the treatment of obesity. For example, anti-obesity drugs include β-3 agonists such as CL-316,243; CB-1 antagonists; neuropeptide Y5 inhibitors; 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.

[396] In addition, the compounds of Formula (I) , Formula (Ia), or Formula (Ib) 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 anatgonists 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.

[397] 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.

[398] 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.

[399] The compounds of Formula (I) , Formula (Ia), and Formula (Ib) 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) , Formula (Ia), or Formula (Ib), 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.

[400] 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

[401] 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.

[402] The total amount of the active ingredient to be administered may generally range from about 0.001 mg/kg to about 200 mg/kg, and preferably from about 0.01 mg/kg to about 200 mg/kg body weight per day. A unit dosage may contain from 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 about 0.01 to about 200 mg/kg. The daily rectal dosage regimen may be from 0.01 to 200 mg/kg of total body weight. The transdermal concentration may be that required to maintain a daily dose of from 0.01 to 200 mg/kg.

[403] 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.

[404] 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.

[405] 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.

[406] 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.

[407] 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.

[408] 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.

[409] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil, or coconut oil; or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or *n*-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

[410] 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.

[411] 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 such as ethanol, isopropanol, or hexadecyl alcohol; glycols such as propylene glycol or polyethylene glycol; glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethyleneglycol) 400; 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 such as a soap or a detergent, suspending agent such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

[412] Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum, and mineral oil. Suitable fatty acids include oleic acid, stearic acid, and isostearic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl

myristate. Suitable soaps include fatty alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

[413] 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.

[414] Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

[415] 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 such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

[416] 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.

[417] 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.

[418] 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.

[419] 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.

[420] 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.

[421] Commonly used pharmaceutical ingredients which may be used as appropriate to formulate the composition for its intended route of administration include: acidifying agents, for example, but are not limited to, acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid; and alkalinizing agents such as, but are not limited to, ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine.

[422] Other pharmaceutical ingredients include, for example, but are not limited to, adsorbents (e.g., powdered cellulose and activated charcoal); aerosol propellants (e.g., carbon dioxide, CCl_2F_2, F_2ClC-$CClF_2$ and $CClF_3$); air displacement agents (e.g., nitrogen and argon); antifungal preservatives (e.g., benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate); antimicrobial preservatives (e.g., benzalkonium chloride, benzethonium chloride, benzyl alcohol,

cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal); antioxidants (e.g., ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite); binding materials (e.g., block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers); buffering agents (e.g., potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate); carrying agents (e.g., acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection); chelating agents (e.g., edetate disodium and edetic acid); colorants (e.g., FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red); clarifying agents (e.g., bentonite); emulsifying agents (but are not limited to, acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate); encapsulating agents (e.g., gelatin and cellulose acetate phthalate); flavorants (e.g., anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin); humectants (e.g., glycerin, propylene glycol and sorbitol); levigating agents (e.g., mineral oil and glycerin); oils (e.g., arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil); ointment bases (e.g., lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment); penetration enhancers (transdermal delivery) (e.g., monohydroxy or polyhydroxy alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas); plasticizers (e.g., diethyl phthalate and glycerin); solvents (e.g., alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation); stiffening agents (e.g., cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax); suppository bases (e.g., cocoa butter and polyethylene glycols (mixtures)); surfactants (e.g., benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate); suspending agents (e.g., agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum); sweetening e.g., aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose); tablet anti-adherents (e.g., magnesium stearate and talc); tablet binders (e.g., acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch); tablet and capsule diluents (e.g., dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium

carbonate, sodium phosphate, sorbitol and starch); tablet coating agents (e.g., liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac); tablet direct compression excipients (e.g., dibasic calcium phosphate); tablet disintegrants (e.g., alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate and starch); tablet glidants (e.g., colloidal silica, corn starch and talc); tablet lubricants (e.g., calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate); tablet/capsule opaquants (e.g., titanium dioxide); tablet polishing agents (e.g., carnuba wax and white wax); thickening agents (e.g., beeswax, cetyl alcohol and paraffin); tonicity agents (e.g., dextrose and sodium chloride);viscosity increasing agents (e.g., alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth); and wetting agents (e.g., heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

[423] 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.

[424] 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.

[425] 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).

BIOLOGICAL ACTIVITY OF THE COMPOUNDS

[426] 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.

[427] 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

[428] 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 minutes. 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.

[429] 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 $MgCl_2$, 0.04% BSA, 20 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 0.5 µg 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 minutes. 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

[430] 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 tetrahydrofuran and sealed in the vials. Vials were sonicated for 30 minutes 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 accomplished by 30 to 100% B buffer in 4 minutes followed by 3 minutes 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% tetrahydrofuran). 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

[431] 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).

[432] 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).

[433] A typical study included 60-80 male C57bl/J6 mice (n = 10/treatment group) with an average body weight of approximately 45 g. Mice were kept in standard animal rooms under controlled temperature and humidity and a 12 hour/12 hour light/dark cycle. Water and food were continuously available. Mice were individually housed. Animals were 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 were assigned to one of 6-8 treatment groups based upon their body weight on baseline. The groups were set up so that the mean and standard error of the mean of body weight were similar.

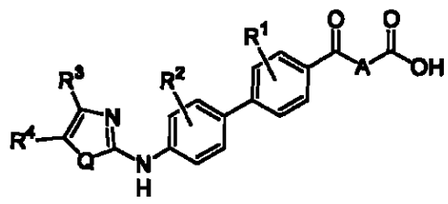
[434] Animals were orally gavaged (5 mL/kg) daily before the dark phase of the light/dark cycle for a pre-determined number of days (typically 8-14 days) with their assigned dose/compound. Body weight, and food and water consumption were measured. Data was analyzed using appropriate statistics following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

[435] Compounds were typically dosed at 5 or10 mg/kg p.o. q.d. as a suspension formulation in 50:50 PEG/water, or p.o. b.i.d. as a suspension formulation in 0.5% methylcellulose, and compounds were considered to be active if a statistically significant reduction in body weight was observed for the treated animals after a treatment period of at least seven days, relative to vehicle-treated control animals.

[436] 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.

What is claimed:

1. A compound of Formula (I)

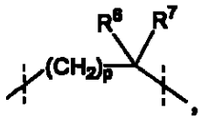


(I)

wherein

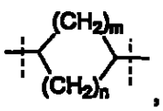
Q is O, S, or NR^5;

A is a linker selected from



wherein p is 1 or 2

and



wherein m is 0 and n is 1, 2, 3, or 4,

or

m is 1 and n is 1, 2, or 3,

and

wherein said linker is optionally substituted by one or two R^8 groups;

R^1 and R^2 are independently selected from hydrogen, halo, (C_1-C_6)alkyl, and (C_1-C_6)alkoxy;

R^3 is selected from

hydrogen,

(C_1-C_6)alkyl optionally substituted by hydroxy,

and

phenyl optionally substituted with (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or halo;

R^4 is selected from hydrogen, nitro, and (C_1-C_6)alkyl;

or

R^3 and R^4 may, when taken together with the carbon atoms to which they are attached, form a benzene ring optionally substituted with up to two substituents 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)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl,

and

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

R^5 is hydrogen or (C_1-C_6)alkyl;

R^6 is hydrogen;

R^7 is hydrogen

or

(C_1-C_6)alkyl optionally substituted with

(C_1-C_6)alkoxy,

bis[(C_1-C_3)alkyl]amino

or

phenyl optionally substituted with halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

or

R^6 and R^7 are both (C_1-C_6)alkyl;

or

R^6 and R^7 may form, together with the carbon atom to which they are attached,

a 3- to 5-membered carbocyclic ring,

or

a 6-membered ring represented by



wherein W is CH_2, $C(CH_3)_2$, O, NR^9, S, or SO_2;

R^8 is $(C_1$-$C_6)$alkyl;

and

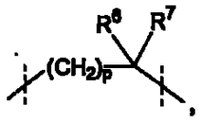
R^9 is hydrogen or $(C_1$-$C_6)$alkyl;

or the pharmaceutically acceptable salts and esters thereof.

2. The compound of claim 1, wherein

Q is NR^5;

A is



wherein p is 1 or 2,

and

wherein said linker is optionally substituted by one or two R^8 groups;

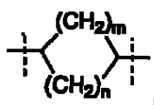
R^3 and R^4 may, when taken together with the carbon atoms to which they are attached, form a benzene ring optionally substituted with up to two substituents selected from halo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, nitro, cyano, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$haloalkoxy, aminocarbonyl, $(C_1$-$C_6)$alkylaminocarbonyl, 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, $(C_1$-$C_4)$alkylsulfonylamino, hydroxy-$(C_2$-$C_4)$alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl; and

R^1, R^2, R^5, R^6, R^7, R^8, R^9, and W are as defined in claim 1.

3. The compound of claim 1, wherein

Q is NR^5;

A is



wherein m is 0 and n is 1, 2, 3, or 4,

or

m is 1 and n is 1, 2, or 3,

and

wherein said linker is optionally substituted by one or two R^8 groups;

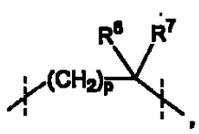
R^3 and R^4 may, when taken together with the carbon atoms to which they are attached, form a benzene ring optionally substituted with up to two substituents selected from halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, cyano, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, aminocarbonyl, (C_1-C_6)alkylaminocarbonyl, 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)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl; and

R^1, R^2, R^5, and R^8 are as defined in claim 1.

4. The compound of claim 1, wherein

Q is O;

A is



wherein p is 1 or 2,

and

wherein said linker is optionally substituted by one or two R^8 groups;

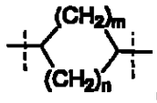
R^3 and R^4 may, when taken together with the carbon atoms to which they are attached, form a benzene ring optionally substituted with up to two substituents selected from halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, cyano, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, aminocarbonyl, (C_1-C_6)alkylaminocarbonyl, 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)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl; and

R^1, R^2, R^6, R^7, R^8, R^9, and W are as defined in claim 1.

5. The compound of claim 1, wherein

Q is O;

A is



wherein m is 0 and n is 1, 2, 3, or 4,

or

m is 1 and n is 1, 2, or 3,

and

wherein said linker is optionally substituted by one or two R^8 groups;

R^3 and R^4 may, when taken together with the carbon atoms to which they are attached, form a benzene ring optionally substituted with up to two substituents 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,

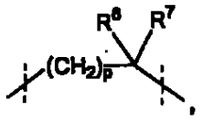
(C_1-C_6)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl; and

R^1, R^2, and R^8 are as defined in claim 1.

6. The compound of claim 1, wherein

Q is S;

A is



wherein p is 1 or 2,

and

wherein said linker is optionally substituted by one or two R^5 groups;

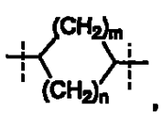
R^3 and R^4 may, when taken together with the carbon atoms to which they are attached, form a benzene ring optionally substituted with up to two substituents selected from halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, cyano, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, aminocarbonyl, (C_1-C_6)alkylaminocarbonyl, 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)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl; and

R^1, R^2, R^6, R^7, R^8, R^9, and W are as defined in claim 1.

7. The compound of claim 1, wherein

Q is S;

A is



wherein m is 0 and n is 1, 2, 3, or 4,

or

m is 1 and n is 1, 2, or 3,

and

wherein said linker is optionally substituted by one or two R^8 groups;

R^3 and R^4 may, when taken together with the carbon atoms to which they are attached, form a benzene ring optionally substituted with up to two substituents selected from halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, nitro, cyano, (C_1-C_4)haloalkyl, (C_1-C_4)haloalkoxy, aminocarbonyl, (C_1-C_4)alkylaminocarbonyl, bis[(C_1-C_4)alkyl]aminocarbonyl, aminosulfonyl, (C_1-C_4)alkylaminosulfonyl, bis[(C_1-C_4)alkyl]aminosulfonyl, (C_1-C_4)alkylcarbonylamino, (C_1-C_4)alkylsulfonylamino, hydroxy-(C_2-C_4)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl; and

R^1, R^2, and R^5 are as defined in claim 1.

8. The compound of claim 1 selected from the group consisting of :

4-[4'-(1H-benzimidazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid;

4-{4'-[(5-methoxy-1H-benzimidazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid;

trans-2-{[4'-(1H-benzimidazol-2-ylamino)-1,1'-biphenyl-4-yl]carbonyl}cyclopentane-carboxylic acid;

trans-2-({4'-[(5-methoxy-1H-benzimidazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-[(4'-{[5-(trifluoromethyl)-1H-benzimidazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl] cyclopentane-carboxylic acid;

trans-2-({4'-[(5,6-difluoro-1H-benzimidazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-(1R,2R)-2-{[4'-(1H-benzimidazol-2-ylamino)-3'-fluoro-1,1'-biphenyl-4-yl]carbonyl}-cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({3'-fluoro-4'-[(5-methoxy-1H-benzimidazol-2-yl)amino]-1,1'-biphenyl-4-yl} carbonyl)cyclopentane-carboxylic acid; and

trans-(1R,2R)-2-[(3'-fluoro-4'-{[5-(trifluoromethyl)-1H-benzimidazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid.

9. The compound of claim 1 selected from the group consisting of :

4-[4'-(1,3-benzoxazol-2-ylamino)-1,1'-biphenyl-4-yl]-4-oxo-2-(2-phenylethyl)butanoic acid;

2,2-dimethyl-4-{4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxobutanoic acid;

4-{4'-[(6-chloro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid;

4-{4'-[(6-methoxy-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid;

2,2-dimethyl-4-{4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxobutanoic acid;

2,2-dimethyl-4-{4'-[(4-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxobutanoic acid;

2,2-dimethyl-4-oxo-4-[4'-(5,6,7,8-tetrahydronaphtho[2,3-d][1,3]oxazol-2-ylamino)-1,1'-biphenyl-4-yl]butanoic acid;

4-{4'-[(5-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid;

4-{4'-[(5-isopropyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid;

2,2-dimethyl-4-oxo-4-{4'-[(5-propyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}butanoic acid;

trans-2-({4'-[(6-chloro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-({4'-[(6-methoxy-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-({4'-[(5-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-({4'-[(5,6-dimethyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-{[4'-(1,3-benzoxazol-2-ylamino)-1,1'-biphenyl-4-yl]carbonyl}cyclopentane-carboxylic acid;

trans-2-({4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-({4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({4'-[(5-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({4'-[(6-chloro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentane-carboxylic acid;

trans-(1R,2R)-2-[(4'-{[5-(trifluoromethyl)-1,3-benzoxazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({4'-[(6-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentane-carboxylic acid;

trans-(1S,2S)-2-({4'-[(6-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentane-carboxylic acid;

trans-2-({4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclohexane-carboxylic acid;

trans-2-({4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclohexane-carboxylic acid;

4-{4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxo-2-(2-phenylethyl) butanoic acid;

trans-2-({3'-fluoro-4'-[(6-methoxy-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentane-carboxylic acid;

trans-2-({4'-[(6-chloro-1,3-benzoxazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}carbonyl)-cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl} carbonyl)cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({3'-fluoro-4'-[(5-fluoro-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl} carbonyl)cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({3'-fluoro-4'-[(6-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl} carbonyl)cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({3'-fluoro-4'-[(5-methyl-1,3-benzoxazol-2-yl)amino]-1,1'-biphenyl-4-yl} carbonyl)cyclopentane-carboxylic acid; and

trans-(1R,2R)-2-[(3'-fluoro-4'-{[5-(trifluoromethyl)-1,3-benzoxazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid.

10. The compound of claim 1 selected from the group consisting of:
4-[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2,2-dimethyl-4-oxobutanoic acid;

4-{4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid;

4-{4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid;

2,2-dimethyl-4-oxo-4-[4'-(1,3-thiazol-2-ylamino)-1,1'-biphenyl-4-yl]butanoic acid;

4-[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]-2-(2-methoxyethyl)-4-oxobutanoic acid;

4-{4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2-(2-methoxyethyl)-4-oxobutanoic acid;

4-{4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2-(2-methoxyethyl)-4-oxobutanoic acid;

trans-2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclobutane-carboxylic acid;

trans-2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

4-{4'-[(5-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid;

2,2-dimethyl-4-{4'-[(6-nitro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxobutanoic acid;

4-{4'-[(4-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid;

trans-(1R,2R)-2-{[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]carbonyl} cyclopentane-carboxylic acid;

trans-2-{[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]carbonyl}cyclopentane-carboxylic acid;

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

2-(2-{4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2-oxoethyl)pentanoic acid;

trans-2-({4'-[(5-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-({4'-[(6-nitro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-({4'-[(4-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

4-{4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2-[2-(dimethylamino) ethyl]-4-oxobutanoic acid;

2-[2-(dimethylamino)ethyl]-4-{4'-[(5-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxobutanoic acid;

2-[2-(dimethylamino)ethyl]-4-{4'-[(6-nitro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxobutanoic acid;

trans-2-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-({4'-[(6-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-({4'-[(6-ethoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

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

trans-(1R,2R)-2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentane-carboxylic acid;

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

2,2-dimethyl-4-{4'-[(5-nitro-1,3-thiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-4-oxobutanoic acid;

4-(4'-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}-1,1'-biphenyl-4-yl)-2,2-dimethyl-4-oxobutanoic acid;

trans-(1R,2R)-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid;

trans-(1S,2S)-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid;

cis-3-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclohexane-carboxylic acid;

cis-3-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclohexane-carboxylic acid;

trans-2-[(4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid;

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

trans-(1R,2R)-2-({4'-[(6-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentane-carboxylic acid;

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

trans-(1S,2S)-2-({4'-[(6-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentane-carboxylic acid;

trans-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-({4'-[(4-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-({4'-[(5-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-[(4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]-cyclopentane-carboxylic acid;

trans-2-({4'-[(5-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-({4'-[(5,7-dimethyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-[(4'-{[6-(methylsulfonyl)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]-cyclopentane-carboxylic acid;

trans-2-({4'-[(5,6-dimethyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

4-{4'-[(6-ethoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-2,2-dimethyl-4-oxobutanoic acid;

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

trans-2-({4'-[(5,7-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopentane-carboxylic acid;

trans-2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopropane-carboxylic acid;

trans-(1R,2R)-2-[(4'-{[5-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)-carbonyl]cyclopentane-carboxylic acid;

trans-2-{[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]carbonyl}cyclopropane-carboxylic acid;

trans-2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclohexane-carboxylic acid;

trans-2-({4'-[(4-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopropane-carboxylic acid;

trans-2-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopropane-carboxylic acid;

trans-2-({4'-[(5,7-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopropane-carboxylic acid;

trans-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclopropane-carboxylic acid;

trans-2-{[4'-(1,3-benzothiazol-2-ylamino)-1,1'-biphenyl-4-yl]carbonyl}cyclobutane-carboxylic acid;

trans-2-({4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclobutane-carboxylic acid;

trans-2-({4'-[(4-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl) cyclobutane-carboxylic acid;

trans-(1R,2R)-2-({4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl} carbonyl)cyclopentane-carboxylic acid;

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

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

trans-(1R,2R)-2-({4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl} carbonyl)cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({3'-fluoro-4'-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl} carbonyl)cyclopentane-carboxylic acid;

trans-2-{[4'-(1,3-benzothiazol-2-ylamino)-3'-fluoro-1,1'-biphenyl-4-yl]carbonyl} cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({4'-[(4,6-difluoro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid;

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

trans-(1R,2R)-2-[(3'-fluoro-4'-{[6-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({3'-fluoro-4'-[(5-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl} carbonyl)cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({3'-fluoro-4'-[(4-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-carbonyl)cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({4'-[(5-chloro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl} carbonyl)cyclopentane-carboxylic acid;

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

trans-(1R,2R)-2-({3'-fluoro-4'-[(6-methyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}-carbonyl)cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({4'-[(5,7-dimethyl-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid;

trans-(1R,2R)-2-({4'-[(5,7-difluoro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl} carbonyl)cyclopentane-carboxylic acid;

trans-(1R,2R)-2-[(3'-fluoro-4'-{[5-(trifluoromethyl)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid;

trans-(1R,2R)-2-[(3'-fluoro-4'-{[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]amino}-1,1'-biphenyl-4-yl)carbonyl]cyclopentane-carboxylic acid;

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

trans-2-{[4'-(1,3-benzothiazol-2-ylamino)-3'-fluoro-1,1'-biphenyl-4-yl]carbonyl} cyclobutane-carboxylic acid;

trans-2-{[4'-(1,3-benzothiazol-2-ylamino)-3'-fluoro-1,1'-biphenyl-4-yl]carbonyl} cyclopropane-carboxylic acid;

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

trans-(1R,2R)-2-({3'-fluoro-4'-[(6-isopropyl-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)cyclopentane-carboxylic acid;

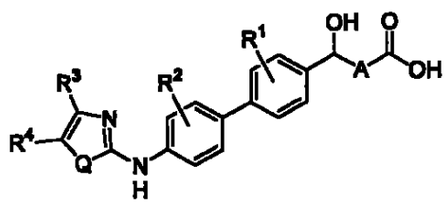
trans-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]-1,1'-biphenyl-4-yl}carbonyl)-cyclopentane-carboxylic acid;

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

4-{4'-[(6-chloro-1,3-benzothiazol-2-yl)amino]-3'-fluoro-1,1'-biphenyl-4-yl}-4-oxo-2-(2-phenylethyl)butanoic acid; and

(1*R*,2*R*)-2-[{3'-fluoro-4'-[(6-fluoro-1,3-benzothiazol-2-yl)amino]biphenyl-4-yl}(hydroxy)-methyl]cyclopentanecarboxylic acid.

11. A compound of Formula (Ia)

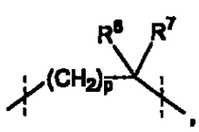


(Ia)

wherein

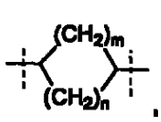
Q is O, S, or NR^5;

A is a linker selected from



wherein p is 1 or 2

and



wherein m is 0 and n is 1, 2, 3, or 4,

or

m is 1 and n is 1, 2, or 3,

and

wherein said linker is optionally substituted by one or two R^6 groups;

R^1 and R^2 are independently selected from hydrogen, halo, (C_1-C_6)alkyl, and (C_1-C_6)alkoxy;

R^3 is selected from

hydrogen,

(C_1-C_6)alkyl optionally substituted by hydroxy,

and

phenyl optionally substituted with (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or halo;

R^4 is selected from hydrogen, nitro, and (C_1-C_6)alkyl;

or

R^3 and R^4 may, when taken together with the carbon atoms to which they are attached, form a benzene ring optionally substituted with up to two substituents 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)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl,

and

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

R^5 is hydrogen or (C_1-C_6)alkyl;

R^6 is hydrogen;

R^7 is hydrogen

or

(C_1-C_6)alkyl optionally substituted with

(C_1-C_6)alkoxy,

bis[(C_1-C_3)alkyl]amino

or

phenyl optionally substituted with halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

or

R^6 and R^7 are both (C_1-C_6)alkyl;

or

R^6 and R^7 may form, together with the carbon atom to which they are attached, a 3- to 5-membered carbocyclic ring,

or

a 6-membered ring represented by



wherein W is CH_2, $C(CH_3)_2$, O, NR^9, S, or SO_2;

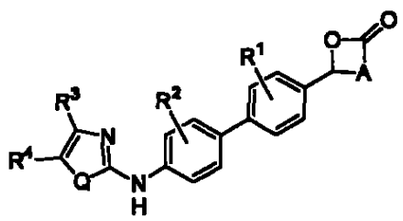
R^8 is (C_1-C_6)alkyl;

and

R^9 is hydrogen or (C_1-C_6)alkyl;

or the pharmaceutical salts and esters thereof.

12. A compound of Formula (Ib)

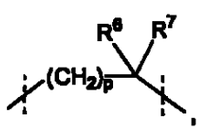


(Ib)

wherein

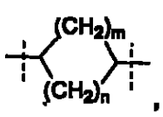
Q is O, S, or NR^5;

A is a linker selected from



wherein p is 1 or 2

and



wherein m is 0 and n is 1, 2, 3, or 4,

or

m is 1 and n is 1, 2, or 3,

and

wherein said linker is optionally substituted by one or two R^8 groups;

R^1 and R^2 are independently selected from hydrogen, halo, (C_1-C_6)alkyl, and (C_1-C_6)alkoxy;

R^3 is selected from

hydrogen,

(C_1-C_6)alkyl optionally substituted by hydroxy,

and

phenyl optionally substituted with (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or halo;

R^4 is selected from hydrogen, nitro, and (C_1-C_6)alkyl;

or

R^3 and R^4 may, when taken together with the carbon atoms to which they are attached, form a benzene ring optionally substituted with up to two substituents 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)alkylsulfonylamino, hydroxy-(C_2-C_6)alkylaminocarbonyl, 1-morpholinylcarbonyl, and 1-piperidinylcarbonyl,

and

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

R^5 is hydrogen or (C_1-C_6)alkyl;

R^6 is hydrogen;

R^7 is hydrogen

or

(C_1-C_6)alkyl optionally substituted with

(C_1-C_6)alkoxy,
bis[(C_1-C_4)alkyl]amino
or
phenyl optionally substituted with halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or cyano;

or

R^6 and R^7 are both (C_1-C_6)alkyl;

or

R^6 and R^7 may form, together with the carbon atom to which they are attached,
a 3- to 5-membered carbocyclic ring,
or
a 6-membered ring represented by



wherein W is CH_2, $C(CH_3)_2$, O, NR^9, S, or SO_2;

R^8 is (C_1-C_6)alkyl;

and

R^9 is hydrogen or (C_1-C_6)alkyl;

or pharmaceutical salts and esters thereof.

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or ester, in combination with a pharmaceutically acceptable carrier.

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

15. The pharmaceutical composition of claim 14, wherein said pharmaceutical agent is an anti-obesity agent selected from the group consisting of β-3 agonists, CB-1 antagonists,

neuropeptide Y5 inhibitors, appetite suppressants, and lipase inhibitors.

16. The pharmaceutical composition of claim 14, wherein said pharmaceutical agent is an agent for the treatment of diabetes selected from the group consisting of insulin, insulin derivatives, PPAR ligands, sulfonylurea drugs, α-glucosidase inhibitors, biguanides, PTP-1B inhibitors, DPP-IV inhibitors, 11-beta-HSD inhibitors, GLP-1 and GLP-1 derivatives, GIP and GIP derivatives, PACAP and PACAP derivatives, and secretin and secretin derivatives.

17. The pharmaceutical composition of claim 14, wherein said pharmaceutical agent is an agent for the treatment of lipid disorders selected from the group consisting of HMG-CoA inhibitors, nicotinic acid, fatty acid lowering compounds, lipid lowering drugs, ACAT inhibitors, bile sequestrants, bile acid reuptake inhibitors, microsomal triglyceride transport inhibitors, and fibric acid derivatives.

18. The pharmaceutical composition of claim 14, wherein said pharmaceutical agent is an anti-hypertensive agent selected from the group consisting of β-blockers, calcium channel blockers, diuretics, renin inhibitors, ACE inhibitors, AT-1 receptor antagonists, ET receptor antagonists, and nitrates.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 8, 9, 10, 11, or 12, or a pharmaceutically acceptable salt or ester, in combination with a pharmaceutically acceptable carrier.

20. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 8, 9, 10, 11, or 12, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more pharmaceutical agents.

21. A method of treating obesity comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 or a composition of claim 13.

22. A method of inducing weight loss comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 or a composition of claim 13.

23. A method of preventing weight gain comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 or a composition of claim 13.

24. A method of treating obesity-related disorders comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 or a composition of claim 13.

25. The method of claim 24, wherein said obesity-related disorder is selected from the group consisting of dyslipidemia, cholesterol gallstones, gallbladder disease, gout, cancer, menstrual abnormalities, infertility, polycystic ovaries, osteoarthritis, sleep apnea, hypertriglyceridemia, Syndrome X, type 2 diabetes, atherosclerotic diseases, hyperlipidemia, hypercholesteremia, low HDL levels, hypertension, cardiovascular disease, coronary heart disease, coronary artery disease, cerebrovascular disease, stroke, and peripheral vessel disease.

26. A method of treating obesity comprising the step of 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.

27. The method of claim 26, wherein the compound of claim 1 and one or more pharmaceutical agents are administered as a single pharmaceutical dosage formulation.

28. A method of treating obesity comprising the step of administering to a subject in need thereof a therapeutically effective amount of a composition of claim 14, 15, 16, 17, or 18.

29. A method of treating obesity-related disorders comprising the step of administering to a subject in need thereof a therapeutically effective amount of a composition of claim 14, 15, 16, 17, or 18.

30. Compounds according to claim 1 for the treatment and/or prophylaxis of obesity and obesity-related disorders.

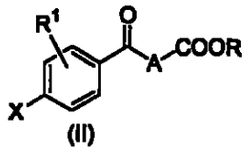
31. Medicament containing at least one compound according to claim 1 in combination with at least one pharmaceutically acceptable, pharmaceutically safe carrier or excipient.

32. Use of compounds according to claim 1 for manufacturing a medicament for the treatment and/or prophylaxis of obesity and obesity -related disorders.

33. Medicaments according to claim 31 for the treatment and/or prophylaxis of obesity.

34. A process for the preparation of a compound of Formula (VIII) comprising the steps of:

reacting a compound of Formula (II)



(II)

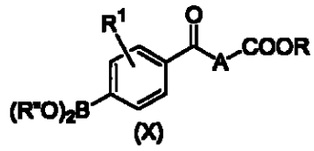
wherein

R is hydrogen or (C_1-C_6)alkyl;

X is Cl, Br, or I; and

R^1 and A are as defined in claim 1;

with a boronic ester reagent to give a compound of Formula (X)



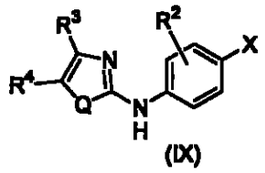
(X)

wherein

R is hydrogen or (C_1-C_6)alkyl; and

R^1 and A are as defined in claim 1;

and coupling the compound of Formula (X) with a compound of Formula (IX)

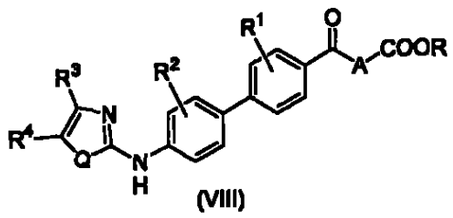


(IX)

wherein

R^2, R^3, R^4, and Q are as defined in claim 1;

in the presence of a palladium catalyst, and optionally in the presence of a base, to give the compound of Formula (VIII)



(VIII)

wherein

R is hydrogen or (C_1-C_6)alkyl,

R^1, R^2, R^3, R^4, A, and Q are as defined in claim 1.

35. The process of claim 34, wherein the boronic ester reagent is pinnacol borane and the base is potassium carbonate.

L97.

PREPARACIÓN Y USO DE DERIVADOS DE ALQUILARILO PARA EL TRATAMIENTO DE LA OBESIDAD

CAMPO DE LA INVENCIÓN

Esta invención se refiere a ciertos compuestos de ácido alquilarílico, composiciones, y métodos para tratar o prevenir la obesidad y enfermedades relacionadas.

ANTECEDENTES DE LA INVENCIÓN

La obesidad, que es un exceso de grasa respecto de la masa corporal magra, es una enfermedad crónica que es sumamente frecuente en la sociedad moderna. Está asociada no sólo con un estigma social, sino también con un lapso de vida reducido y numerosos problemas médicos, incluyendo un desarrollo psicológico adverso, arteriopatía coronaria, hipertensión, accidente cerebrovascular, diabetes, hiperlipidemia y algunos tipos de cáncer. (*ver, por ej.*, 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).

La obesidad continúa siendo un problema, y el tratamiento se ha limitado. Por lo tanto, existe la necesidad de desarrollar productos farmacéuticos y regímenes de tratamiento efectivos en el alivio de la obesidad.

Una característica típica de la obesidad es un aumento en la masa de tejido adiposo blanco (TAB) que se debe en gran medida a la acumulación de triacilgliceroles. Este aumento en la masa de TAB es un contribuyente clave en las

complicaciones asociadas con la obesidad. Las diacilglicerol O-aciltransferasas (DGATs, EC 2,3,1,2) son enzimas unidas a la membrana que catalizan el paso terminal de la biosíntesis de los triglicéridos. Se han caracterizado dos enzimas que presentan actividad de DGAT: DGAT-1 (diacilglicerol O-aciltransferasa tipo 1) (*ver, por ej.,* Patente de los Estados Unidos No. 6.100.077; Cases, et al., Proc. Nat. Acad. Sci. 95: 13018-13023, 1998) y DGAT-2 (diacilglicerol O-aciltransferasa tipo 2) (Cases, et al., J. Biol. Chem. 276: 38870-38876, 2001). Las DGAT-1 y DGAT-2 no exhiben una significativa identidad por la secuencia de la proteína. Es importante mencionar que los ratones desprovistos de DGAT-1 se toman obesos cuando se los provoca con una dieta con alto contenido graso en contraste con sus crías de tipo salvaje (Smith, et al., Nature Genetics 25: 87-90, 2000). Los ratones desprovistos de DGAT-1 presentan niveles reducidos de glucosa plasmática post-prandial y exhiben un mayor gasto de energía, pero tienen niveles normales de triglicéridos séricos (Smith, et al., 2000), lo que se debe, posiblemente, a la actividad preservada de DGAT-2. Dado que la DGAT-1 se expresa en el intestino y el tejido adiposo (Cases, et al., 1998), existen dos mecanismos posibles para explicar la resistencia de los ratones desprovistos de DGAT-1 a la obesidad inducida por dietas. Primero, la supresión de la actividad de DGAT-1 en el intestino puede bloquear la formación y exportación del triacilglicerol de las células intestinales en la circulación a través de partículas quilomicrónicas. Segundo, producir el knock-out de la actividad de DGAT-1 en los adipocitos puede reducir la deposición de triacilglicerol en el TAB. El fenotipo del ratón desprovisto de DGAT-1, junto con los resultados de nuestros estudios con inhibidores de DGAT-1 en ratones obesos inducidos por dietas (OID), indican que un inhibidor de DGAT-1

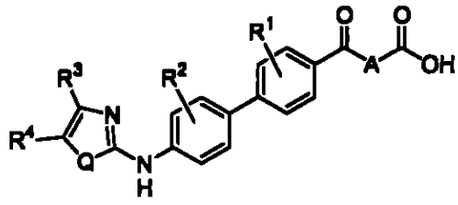
199.

tiene utilidad para el tratamiento de la obesidad y las complicaciones asociadas con la obesidad.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La invención se refiere a derivados de ácido alquilarílico, y sus sales y ésteres farmacéuticos, que tienen utilidad en la inhibición de DGAT-1 (diacilglicerol O-aciltransferasa tipo 1) y en el tratamiento de la obesidad y enfermedades relacionadas.

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

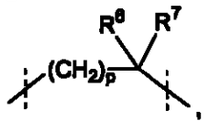


(I)

en el cual

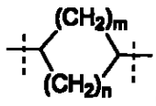
Q es O, S, o NR^5;

A es una ligadura seleccionada de



en la cual p es 1 o 2

y



en la cual m es 0 y n es 1, 2, 3, o 4,

o

m es 1 y n es 1, 2, o 3,

h

en el cual dicha ligadura está sustituida en forma opcional por uno o dos grupos R^6;

R^1 y R^2 se seleccionan en forma independiente de hidrógeno, halo, alquilo (C_1-C_6), y alcoxi (C_1-C_6);

R^3 se selecciona de

hidrógeno,

alquilo (C_1-C_6) sustituido en forma opcional por hidroxi,

y

fenilo sustituido en forma opcional con alquilo (C_1-C_6), alcoxi (C_1-C_6), o halo;

R^4 se selecciona de hidrógeno, nitro, y alquilo (C_1-C_6);

o

R^3 y R^4 pueden, cuando se los toma junto con los átomos de carbono a los cuales están unidos, formar un anillo bencénico sustituido en forma opcional con hasta dos sustituyentes seleccionados de

halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), nitro, ciano, haloalquilo (C_1-C_6), haloalcoxi (C_1-C_6), aminocarbonilo, alquilaminocarbonilo (C_1-C_6), bis[alquil (C_1-C_6)]aminocarbonilo, aminosulfonilo, alquilaminosulfonilo (C_1-C_6), bis[alquil (C_1-C_6)]aminosulfonilo, alquilcarbonilo (C_1-C_6), alquilsulfonilamino (C_1-C_6), hidroxi-alquilamino (C_2-C_6)carbonilalquilsulfonilamino (C_1-C_6), 1-morfolinilcarbonilo, y 1-*piperidinilcarbonilo*,

y

cuando dos de dichos sustituyentes del anillo bencénico son alquilo (C_1-C_6) y están unidos a átomos de carbono adyacentes del anillo bencénico, pueden unirse para formar un anillo carbocíclico de 5-7 miembros;

R^5 es hidrógeno o alquilo (C_1-C_6);

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201

R^6 es hidrógeno;

R^7 es hidrógeno o alquilo (C_1-C_6) sustituido en forma opcional con

alcoxi (C_1-C_6),

bis[alquil (C_1-C_3)]amino

o

fenilo sustituido en forma opcional con halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), o ciano;

o

R^6 y R^7 son ambos alquilo (C_1-C_6);

o

R^6 y R^7 pueden formar, junto con el átomo de carbono al cual están unidos,

un anillo carbocíclico de 3 a 5 miembros,

o

un anillo de 6 miembros representado por



en el cual W es CH_2, $C(CH_3)_2$, O, NR^9, S, o SO_2;

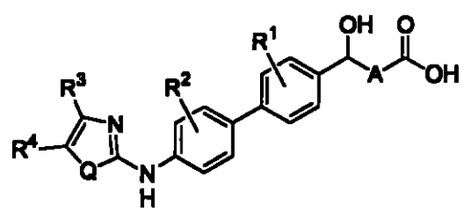
R^8 es alquilo (C_1-C_6);

y

R^9 es hidrógeno o alquilo (C_1-C_6);

o sus sales y ésteres aceptables desde el punto de vista farmacéutico.

Una segunda realización de esta invención es un compuesto de Fórmula (Ia)



(Ia)

~~202~~

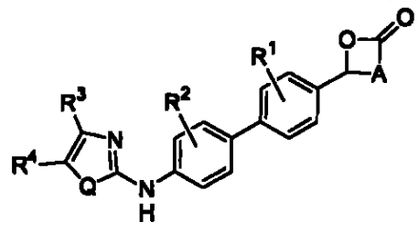
202

en el cual

Q, A, y R^1-R^4 tienen los significados descritos anteriormente para la Fórmula (I)

o sus sales y ésteres farmacéuticos.

Una tercera realización de la invención es un compuesto de Fórmula (Ib)



(Ib)

en el cual

Q, A, y R^1-R^4 tienen los significados descritos anteriormente para la Fórmula (I),

o sus sales y ésteres farmacéuticos.

Ejemplos de la invención pueden encontrarse en los Ejemplos descritos a continuación y en las Tablas 1 y 2. Se pretende que los compuestos descritos en los Ejemplos sean representativos de la invención, y se comprenderá que el alcance de la invención no se limita por el alcance de los ejemplos. Aquellos expertos en el arte reconocerán que la invención puede practicarse con variaciones de las estructuras, los materiales, las composiciones y los métodos descritos, y dichas variaciones se consideran dentro del ámbito de la invención.

Los términos identificados anteriormente tienen el siguiente significado en todo este texto:

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

Los términos "alquilo (C_1-C_6)," y "alquilo (C_2-C_6)" significan grupos hidrocarbonados saturados lineales o ramificados que tienen desde aproximadamente 1 hasta aproximadamente 6 átomos de carbono, o desde 2 hasta aproximadamente 6 átomos de carbono, respectivamente. El grupo

hidrocarbonado puede incluir, además, un radical alquilo como parte del grupo alquilo. Dichos grupos incluyen, sin carácter limitativo, grupos metilo, etilo, *n*-propilo, isopropilo, butilo, isobutilo, pentilo, hexilo, ciclopropilo, ciclohexilo, ciclopropil-metilo, y ciclopentil-metilo.

El término "alcoxi (C_1-C_6)" significa un grupo hidrocarbonado saturado lineal o ramificado que tiene desde aproximadamente 1 hasta aproximadamente 6 átomos de carbono, dicho grupo está unido a un átomo de oxígeno. El átomo de oxígeno es el átomo a través del cual el sustituyente alcoxi está unido al resto de la molécula. El grupo hidrocarbonado puede incluir, además, un radical alquilo cíclico como parte del grupo alquilo. Dichos grupos incluyen, sin carácter limitativo, metoxi, etoxi, *n*-propoxi, isopropoxi, *n*-butoxi, *n*-hexiloxi, 3,3-dimetilpropoxi, ciclopropoxi, ciclopropilmetoxi, ciclopentiloxi, y similares.

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

Los términos "aminocarbonilo," "alquilaminocarbonilo (C_1-C_6)," y "bis[alquil (C_1-C_6)]aminocarbonilo," significan un grupo carbonilo [C(=O)] sustituido por un átomo de nitrógeno en el cual el átomo de nitrógeno es no sustituido, sustituido por

un único grupo (C_1-C_6), o por dos grupos alquilo (C_1-C_6), respectivamente. El grupo carbonilo es el punto de unión del sustituyente al resto de la molécula. Dichos grupos incluyen carboxamido [$NH_2C(=O)$-], N-metilcarboxamido [$CH_3NHC(=O)$], N-metil-N-propilcarboxamido [$CH_3CH_2CH_2N(CH_3)C(=O)$-] y N,N-dietilcarboxamido [$(CH_3CH_2)_2NC(=O)$-], y similares.

El término "hidroxi-alquilamino (C_2-C_6)carbonilalquilsulfonilamino (C_1-C_6)" significa un grupo carbonilo [C(=O)] sustituido por un átomo de nitrógeno en el cual el átomo de nitrógeno está sustituido por un único grupo (C_2-C_6), y dicho alquilo está sustituido en forma adicional por un grupo hidroxi. Dichos grupos incluyen 2-hidroxietilamido, 3-hidroxdpropilamido, 4-hidroxihexilamido, y similares.

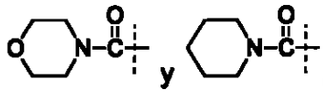
Los términos "aminosulfonilo," "alquilaminosulfonilo (C_1-C_6)," y "bis[alquil (C_1-C_6)]aminosulfonilo" significan un grupo $S(=O)_2$ sustituido por un átomo de nitrógeno en el cual el átomo de nitrógeno es no sustituido, sustituido por un único grupo alquilo (C_1-C_6), o por dos grupos alquilo (C_1-C_6), respectivamente. El grupo $S(=O)_2$ es el punto del unión del sustituyente al resto de la molécula. Dichos grupos incluyen aminosulfonilo [$NH_2S(=O)_2$-], N-metilaminosulfonil-[$CH_3NHS(=O)_2$], N-metil-N-propilaminosulfonilo [$CH_3CH_2CH_2N(CH_3)S(=O)_2$-] y N,N-dietilaminosulfonilo [$(CH_3CH_2)_2NS(=O)_2$-], y similares.

El término "alquilcarbonilo (C_1-C_6)" significa un grupo amino en el cual el átomo de nitrógeno está sustituido por un grupo carbonilo, y dicho grupo carbonilo está sustituido en forma adicional 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 incluyen grupos acetilamino [$CH_3C(=O)NH$-], propanoilamino [$CH_3CH_2C(=O)NH$-], e *i*-butanoilamino [$(CH_3)_2CHC(=O)NH$-], y similares.

El término "alquilsulfonilamino (C_1-C_6)" significa un grupo amino en el cual el átomo de nitrógeno está sustituido por un grupo sulfonilo [$S(=O)_2$], y dicho grupo sulfonilo está sustituido en forma adicional por un grupo alquilo (C_1-C_6). El átomo

~~205~~
205

de nitrógeno es el punto de unión del sustituyente al resto de la molécula. Dichos grupos incluyen grupos metilsulfonilamino [$CH_3S(=O)_2NH$-], propilsulfonilamino [$CH_3CH_2CH_2S(=O)_2NH$-], e *i*-propilsulfonilamino [$(CH_3)_2CHS(=O)_2NH$-], y similares.

Los términos "1-morfolinilcarbonilo" y "1-piperidinilcarbonilo" significan  y , respectivamente.

El término "sustituido en forma opcional" significa que el resto así modificado puede tener desde ninguno hasta el número más elevado de sustituyentes indicados. Cada sustituyente puede reemplazar cualquier átomo de hidrógeno en el resto así modificado, en tanto el reemplazo sea químicamente posible y químicamente estable. Cuando existan dos o más sustituyentes en cualquier resto, cada sustituyente se elige en forma independiente de cualquier otro sustituyente y puede, en consecuencia, ser igual o diferente.

Cuando se describe que un resto está sustituido, puede tener uno o más de los sustituyentes indicados que pueden estar ubicados en cualquier posición disponible del resto. Cuando existan dos o más sustituyentes en cualquier resto, cada término se definirá en forma independiente de cualquier otro caso.

Las sales representativas de los compuestos de Fórmula (I), Fórmula (Ia), y Fórmula (Ib) incluyen las sales no tóxicas y las sales de amonio cuaternario convencionales que se forman, por ejemplo, a partir de ácidos o bases orgánicos o inorgánicos por medios conocidos en el arte. Por ejemplo, dichas sales de adición con ácido incluyen, acetato, adipato, ascorbato, aspartato, benzoato, bencensulfonato, bisulfato, butirato, citrato, alcanforato, alcanforsulfonato, cinamato, ciclopentanpropionato, digluconato, dodecilsulfato, etansulfonato, fumarato, glucoheptanoato,

glicerofosfato, 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 alcalinas incluyen sales de metal alcalino, tales como sales de potasio y sodio, sales de metales alcalino-térreos tales como sales de calcio y magnesio, y sales de amonio con bases orgánicas tales como sales de diciclohexilamina y *N*-metil-D-glucamina. En forma adicional, los grupos que contienen nitrógeno básico pueden cuaternizarse con agentes tales como haluros de alquilo inferior tales como cloruros, bromuros y yoduros de metilo, etilo, propilo y butilo; dialquil sulfatos como dimetil, dietil, y dibutil sulfato; y diamil sulfatos, 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 otros.

Los ésteres en la presente invención son derivados no tóxicos, aceptables desde el punto de vista farmacéutico de los compuestos de Fórmula (I) , Fórmula (Ia), y Fórmula (Ib). Esto incluye, por ejemplo, derivados de éster de compuestos que contienen hidroxilo de Fórmula (I) , Fórmula (Ia), y Fórmula (Ib) preparados con ácido acético, benzoico, mandélico, esteárico, láctico, salicílico, hidroxinaftoico, glucoheptanoico, y glucónico. Esto incluye, además, por ejemplo, derivados de éster de compuestos que contienen ácido carboxílico de Fórmula (I) y Fórmula (Ia) preparados con alcoholes aceptables desde el punto de vista farmacéutico. Los alcoholes aceptables desde el punto de

vista farmacéutico incluyen, sin carácter limitativo metanol, etanol, isopropanol, butanol, 2-metilpropanol, 2-metoxietanol, 2-(dimetilamino)etanol, 2-(dietilamino)etanol, 2-(1-piperidinil)etanol, 2-(1-morfolinil)etanol, ácido hidroxiacético, N,N-dimetilglicolamida, hidroxiacetona, y similares. Resultará obvio para aquellos expertos en el arte que los compuestos de Fórmula (Ia) son ácidos hidroxilados y por lo tanto pueden formar ésteres cíclicos (es decir, lactonas). Estos ésteres, incluyendo aquellos representados por la Fórmula (Ib), se incluyen dentro del alcance de la invención. Los compuestos de Fórmula (I), Fórmula (Ia), y Fórmula (Ib) pueden esterificarse a través de una variedad de procedimientos convencionales conocidos por aquellos expertos en el arte. Una persona experta en el arte sabrá fácilmente cómo llevar a cabo con éxito estos y otros métodos de esterificación.

Puede ser necesario proteger los grupos sensibles o reactivos en los compuestos de Fórmula (I), Fórmula (Ia), y Fórmula (Ib) durante cualesquiera de los métodos anteriores para formar ésteres, y los grupos protectores pueden agregarse y eliminares a través de métodos convencionales conocidos en el arte.

Los compuestos de esta invención pueden, ya sea por su naturaleza de centros asimétricos o por rotación restringida, estar presentes en forma de isómeros. Puede existir cualquier isómero en el cual el centro asimétrico se encuentre en la configuración (*R*), (*S*), o (*R,S*).

Se apreciará, además, que cuando se encuentren presentes dos o más centros asimétricos en los compuestos de la invención, que con frecuencia serán posibles varios diasterómeros y enantiómeros de las estructuras simplificadas, y que los diasterómeros puros y los enantiómeros puros representan las realizaciones preferidas. Se pretende que los

estereoisómeros puros, los diasterómeros puros, los enantiómeros puros y sus mezclas, se encuentren dentro del alcance de la invención.

Todos los isómeros, ya sea separados, puros, parcialmente puros o en mezcla racémica, de los compuestos de esta invención se incluyen dentro del alcance de esta invención. La purificación de dichos isómeros y la separación de dichas mezclas isoméricas pueden lograrse a través de técnicas estándar conocidas en el arte.

Los isómeros geométricos por naturaleza de los sustituyentes alrededor de un enlace o un anillo pueden estar presentes en forma cis (= *Z*-) o trans (= *E*-), y ambas formas isoméricas se incluyen dentro del alcance de esta invención.

El proceso particular que se utilizará en la preparación de los compuestos de esta invención depende del compuesto específico deseado. Factores tales como la selección de los restos específicos y los sustituyentes específicos en los diferentes restos, cumplen una función importante en la vía que debe seguirse en la preparación de los compuestos específicos de esta invención. Estos factores son ampliamente reconocidos por un experto en el arte.

Para la síntesis de cualquier compuesto particular, una persona experta en el arte reconocerá que puede requerirse el uso de grupos protectores apropiados para la síntesis de compuestos que contienen determinados sustituyentes. Puede encontrarse una descripción de los grupos protectores apropiados y los métodos apropiados de agregar y eliminar dichos grupos, por ejemplo, en Protective Groups in Organic Synthesis, Second Edition, T. W. Greene, John Wiley and Sons, New York, 1991.

En los esquemas de reacción que siguen, una persona experta en el

arte reconocerá que los reactivos y los solventes realmente utilizados pueden seleccionarse de varios solventes y reactivos conocidos en el arte como equivalentes efectivos. Cuando se muestran reactivos o solventes específicos en un esquema de reacción, por consiguiente, se consideran ejemplos ilustrativos de las condiciones deseables para la ejecución de ese esquema de reacción particular. Las abreviaturas no identificadas en el texto que sigue se enumeran más adelante bajo el título "Abreviaturas y Siglas."

Otro objetivo de esta invención es proveer métodos para realizar los compuestos de la invención. Los compuestos pueden prepararse a partir de materiales ampliamente disponibles a través de los métodos definidos en el esquema de reacción y en los Ejemplos que siguen, a través de modificaciones obvias a los mismos.

Preparación General de los Compuestos de la Invención

La preparación de los compuestos de la presente invención que tienen la Fórmula (I), puede lograrse a través de cualquiera de los dos métodos generales que se muestran a continuación en el Esquema de Reacción 1 y Esquema de Reacción 2.

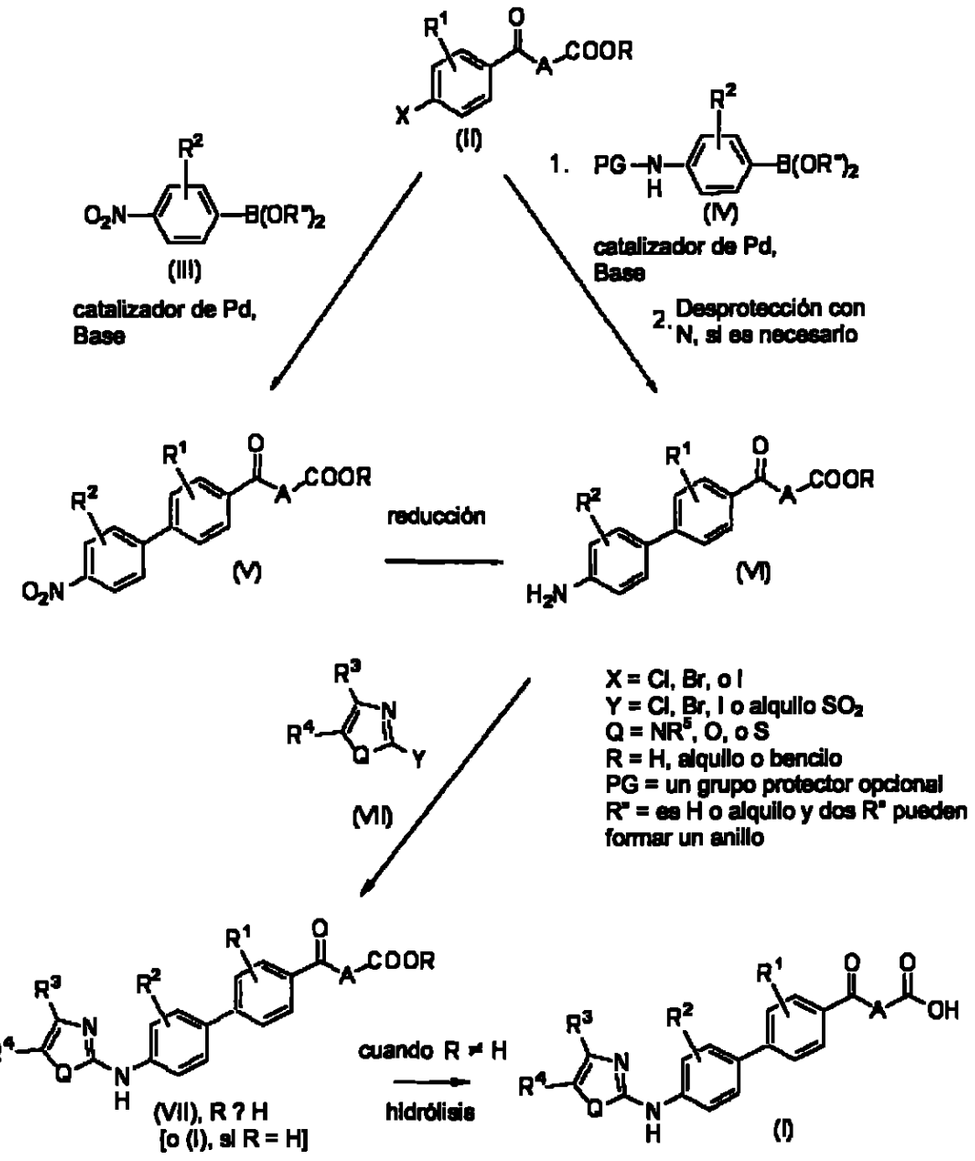
En el Esquema de Reacción 1, una reacción de acoplamiento del compuesto de Fórmula (II) con ácido nitrofenilborónico o éster borónico de Fórmula (III), en presencia de un catalizador de paladio tal como $PdCl_2(dppf)$, da el intermediario de Fórmula (V). La reducción del grupo nitro al compuesto de Fórmula (V) puede lograrse por medios estándares tales como ácido acético/ hierro para suministrar el correspondiente amino compuesto de Fórmula (VI). Una vía alternativa a los compuestos de Fórmula (VI) es llevar a cabo una reacción de acoplamiento del compuesto de Fórmula (II) catalizada con paladio con el ácido anilino borónico/éster borónico opcionalmente protegido de Fórmula (IV), seguido de desprotección, si es

necesario, para suministrar el compuesto de Fórmula (VI) en forma directa. Los reactivos ácido nitro o amino borónico/éster borónico (III) y (IV), respectivamente, se encuentran disponibles en el mercado o pueden prepararse a partir de los halonitrobencenos correspondientes ampliamente disponibles por medios conocidos en el arte.

Luego, se hace reaccionar el compuesto de Fórmula (VI) con el heterociclo 2-halo sustituido y compuestos relacionados de Fórmula (VII) para dar los compuestos de Fórmula (VIII) en los que $R \neq H$ o Fórmula (I) cuando R = H. Los compuestos de Fórmula (VIII) pueden hidrolizarse en condiciones estándar de hidrólisis del éster para dar los compuestos de Fórmula (I).

211

Esquema de Reacción 1



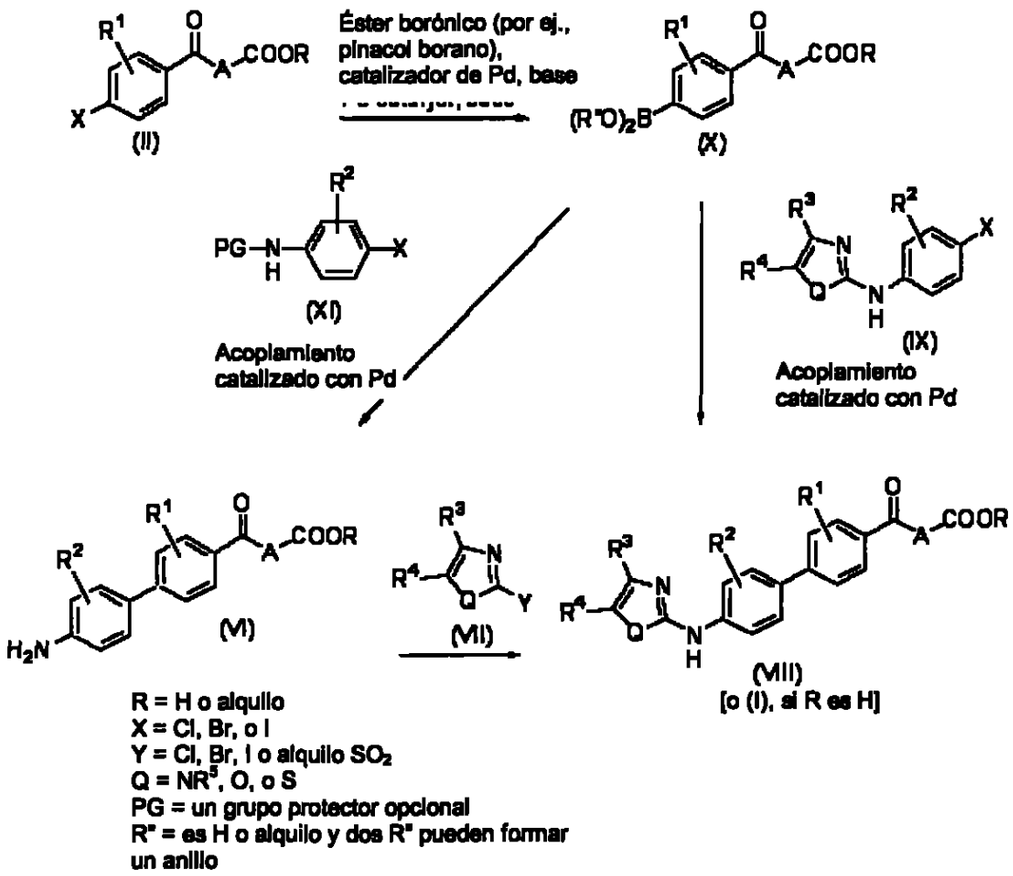
Las alternativas para la preparación de los compuestos de Fórmula (VIII), útiles cuando los ácidos borónicos o ésteres borónicos de Fórmulas (III) y (IV) no son accesibles fácilmente, se muestran en el Esquema de Reacción 2 a continuación. La preparación del éster borónico de Fórmula (X) a partir del

212.

correspondiente compuesto de Fórmula (II) se logra por reacción de (II) con un reactivo éster borónico tal como pinacol borano para obtener el intermediario de Fórmula (X). Este reactivo ácido/éster borónico de Fórmula (X) puede acoplarse con el 2-anilino-heterociclo de Fórmula (IX) en presencia de un catalizador de paladio y una base tal como carbonato de potasio, para dar el intermediario de Fórmula (VIII). El compuesto de Fórmula (VIII) puede prepararse, además, llevando a cabo una reacción de acoplamiento de (X) con la haloanilina opcionalmente protegida de Fórmula (XI), brindando una vía adicional al intermediario de Fórmula (VI). La hidrólisis de (VIII), como se describe en el Esquema de Reacción 1, da el compuesto de Fórmula (I).

Esquema de Reacción 2

213

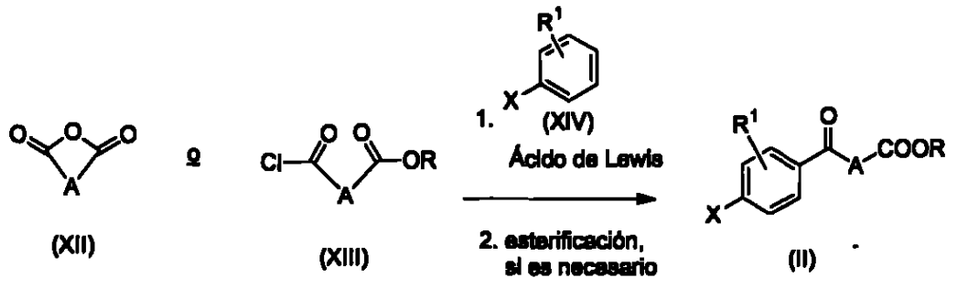


R = H o alquilo
X = Cl, Br, o I
Y = Cl, Br, I o alquilo SO_2
Q = NR^5, O, o S
PG = un grupo protector opcional
R" = es H o alquilo y dos R" pueden formar un anillo

Los compuestos de Fórmula (II) pueden prepararse a partir de un anhídrido ampliamente disponible de Fórmula (XII) o un cloruro de ácido-éster de Fórmula (XIII) a través de una reacción de acilación estándar de Friedel-Crafts como se muestra en el Esquema de Reacción 3.

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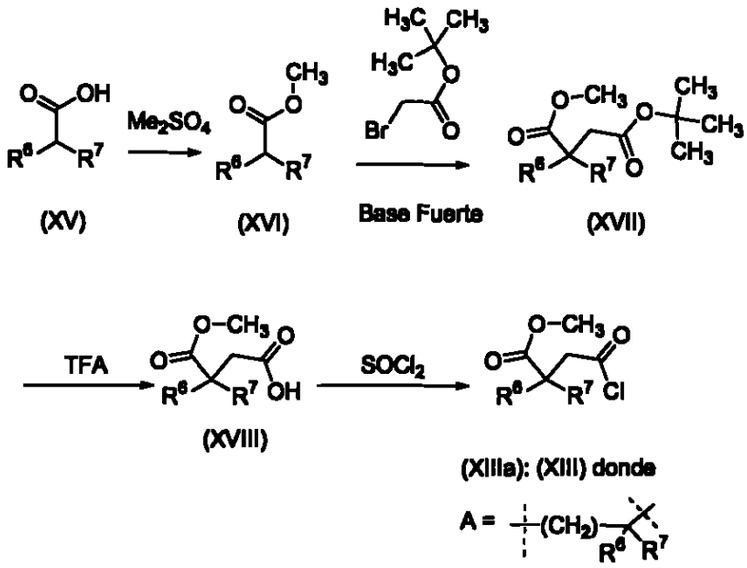
Esquema de Reacción 3

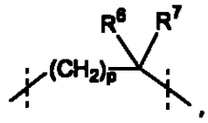


Los intermediarios de Fórmula (XIII) se encuentran disponibles en el mercado o pueden prepararse de un modo directo a partir de precursores ampliamente disponibles. Un método general de preparación de la Fórmula (XIIIa) [(XIII) donde A = -$(CH_2)C(R^6)(R^7)$-] se presenta en el Esquema de Reacción 4. La esterificación de un ácido carboxílico sustituido de Fórmula (XV) da un éster sustituido de Fórmula (XVI); la alquilación del éster con bromoacetato de *t*-butilo da el éster de Fórmula (XVII). La eliminación selectiva del grupo *t*-butilo en condiciones ácidas normales da el monoéster de monoácido de Fórmula (XVIII) que puede convertirse por medios estándar (por ej., $SOCl_2$) en el cloruro de ácido-éster de Fórmula (XIIIa).

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Esquema de Reacción 4

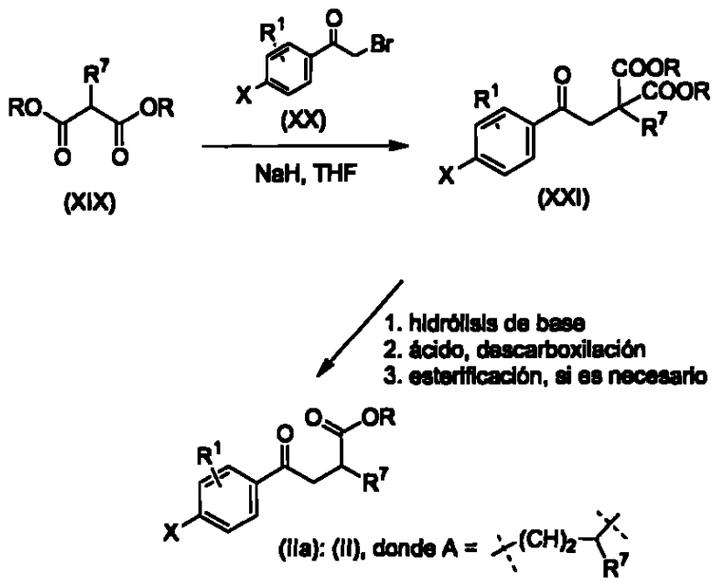


Los compuestos de Fórmula (II) en los cuales A es  , R^6 es H, y p es 1, pueden prepararse como se muestra en el Esquema de Reacción 5, a través de la alquilación de un éster masónico sustituido de Fórmula (XIX) con el bromuro de fenacilo de Fórmula (XX), en presencia de una base fuerte tal como hidruro de sodio, para dar el intermediario de Fórmula (XXI). La hidrólisis y la descarboxilación de (XXI) dan el compuesto de Fórmula (IIa) [(II) donde A es $-(CH_2)CH(R^7)-$].

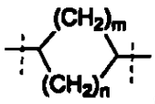
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Esquema de Reacción 5



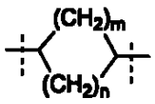
La preparación de compuestos de Fórmula (II) en los cuales A es



, m es 0,

y n es 1, 2, 3, o 4, y está sustituido en forma opcional por hasta dos grupos R^8 se sintetiza en el Esquema de Reacción 6. Este Esquema de Reacción ilustra un método general de obtención de los compuestos de Fórmula (II) donde son posibles los estereoisómeros, y muestra específicamente la preparación de los diastereómeros (*R,R*) de Fórmula (IId) y Fórmula (IIe).

En el Esquema de Reacción 6, el anhídrido de Fórmula (XIIb) [Fórmula (XII) donde A es



,

m es 0, n es 1, 2, 3, o 4, y está sustituido en forma opcional por hasta dos grupos R^8] se convierte en dos etapas en el compuesto de Fórmula (XIIIb) [Fórmula (XIII)

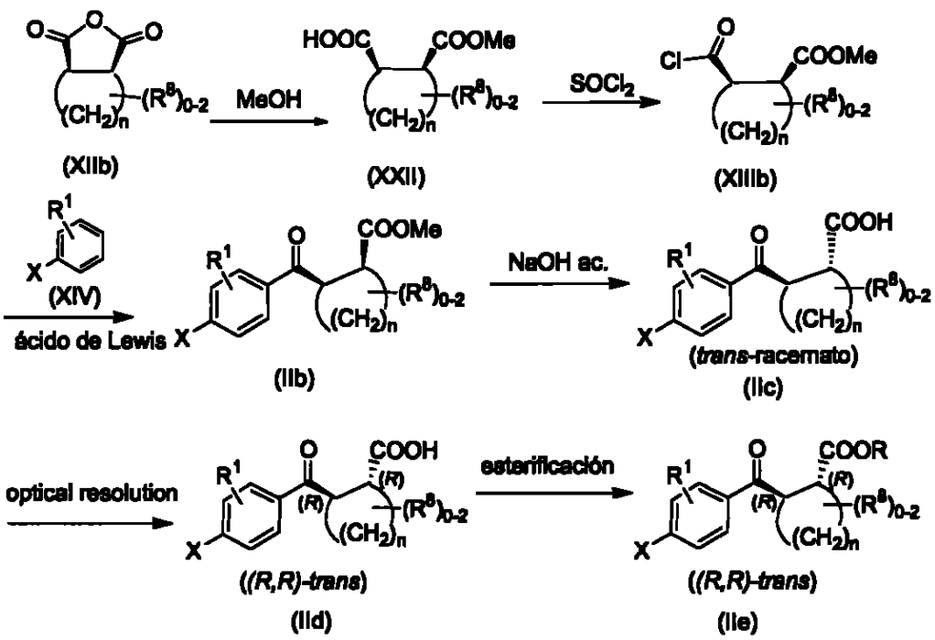
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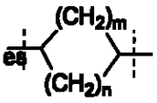
donde A se definió con anterioridad para la Fórmula (XII)]. Se sigue el método del Esquema de Reacción 3 para preparar el compuesto de Fórmula (IIb) a partir de (XIIIb). La Fórmula (IIb) puede convertirse en el compuesto de Fórmula (IIc) por hidrólisis alcalina. Si se desea, puede resolverse (IIc) en sus antípodas ópticas por medios estándar, por ejemplo a través de la cristalización selectiva de sus sales diastereómeras con una base óptimamente activa tal como (*R*)- o (*S*)-1-feniletilamina, y liberando el compuesto óptimamente purificado por acidificación de la sal. Por consiguiente, el compuesto de Fórmula (IId) puede prepararse y convertirse en el correspondiente éster de Fórmula (Ie).

Se debe comprender que los intermediarios de Fórmulas (IIb) a (IIe) pueden llevarse a cabo en forma individual a los correspondientes compuestos de Fórmula (I) a través de los métodos definidos en los Esquemas de Reacción 1 y 2 anteriores, permitiendo de este modo los diferentes compuestos diasteroméricos de Fórmula (I).

Esquema de Reacción 6

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La Fórmula (IIb) - (IIe) representa Fórmula (II) donde A es  ,

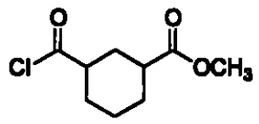
m es 0; n es 1, 2, 3, o 4; y A está sustituido en forma opcional por dos grupos R^8

Otros compuestos de Fórmula (II) pueden prepararse a través de métodos conocidos en el arte o por los métodos descritos aquí, por ejemplo, usando los compuestos 1 (preparado como se describe en McDonald, et al., J. Org. Chem. 35: 2666-2669, 1970), 2 (preparado como se describe en Hronowski, et al., Can. J. Chem, 66: 61-70, 1988), 3 (preparado como se describe en Chung, et al., Bioorg. Med. Chem. Lett. 5: 1097-1102, 1995; Seetz, et al., Rec. Trav. Chim. Pays-Bas 107: 160-162, 1988), 4 (preparado como se describe en Jun, et al., Bull. Korean Chem. Soc. 9: 206-209, 1988); 5 (*ver, por ej.*, los métodos descritos en la Patente de los Estados Unidos No. 6,562,828); 6 y 7 (*ver, por ej.*, los métodos descritos en Carlon, et al., Org. Prep. Proc. Int. 9: 94-96,

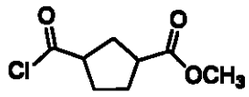
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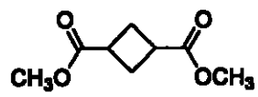
1977; Patente de los Estados Unidos No. 3.256.277; Bushweller, et al.,. J. Org. Chem. 54: 2404-2409, 1989).



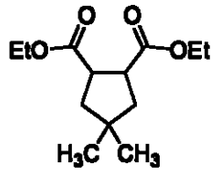
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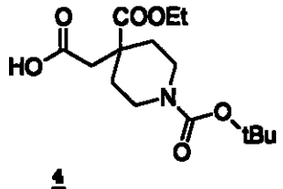
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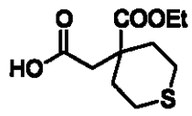
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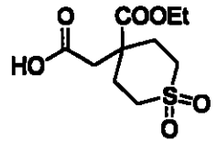
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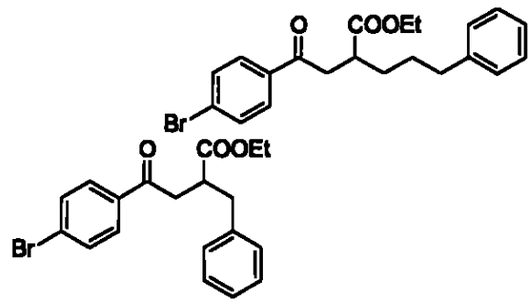


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Además, los compuestos de Fórmula (II) pueden prepararse aplicando otros métodos conocidos en el arte. Por ejemplo, para preparar los siguientes compuestos específicos de Fórmula (II), designados 8-13, pueden emplearse los siguientes métodos: 8 (*ver, por ej.*, WO 9615096 y Patente de los Estados Unidos No. 5.789.434); 9 (*ver, por ej.*, los métodos descritos en WO 9717317); 10 (*ver, por ej.*, los métodos descritos en van der Mey, et al., J. Med. Chem. 44: 2511-2522, 2001; Gaare, et al., Acta Chem. Scand. 51: 1229-1233, 1997; Kuchar, et al., Coll. Czech. Chem. Commun. 51:2617-25, 1986); 11 (*ver, por ej.*, los métodos descritos en Kawamatsu, et al., Arzneim. Forsch. 30: 454-459, 1980; Bajaj, et al., J. Indian Chem. Soc. 52: 1076-1078, 1975); 12 y 13 (*ver, por ej.*, los métodos descritos en WO 9615096, y Sen, et al, Indian J. Chem. 23B: 821-824, 1984).

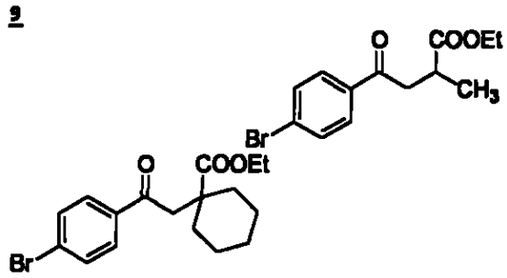
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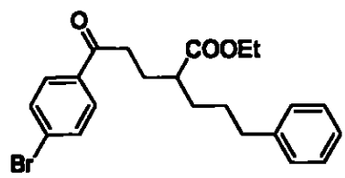
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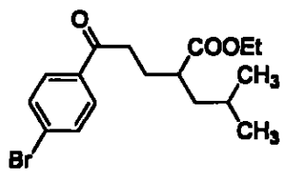
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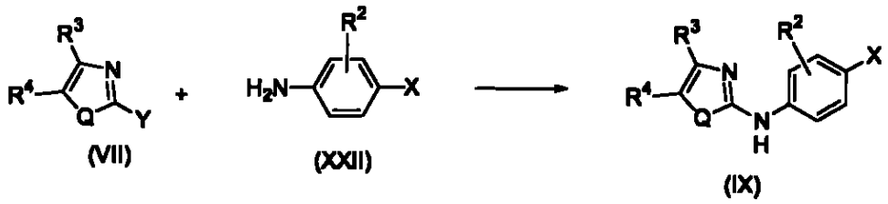
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Los compuestos de Fórmula (IX) pueden prepararse por reacción de una anilina de Fórmula (XXII) permitiendo la reacción con un compuesto de Fórmula (VII), en general con calentamiento en un solvente inerte. Este método se ilustra en el Esquema de Reacción 7.

Esquema de Reacción 7

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221



(VII) (XXII) (IX)

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

Otros compuestos de Fórmula (IX) pueden prepararse a través de otros métodos conocidos en el arte, por ejemplo, mediante la reacción de un tiocianato de 2-oxoetilo con una anilina de Fórmula (XXII) para formar un 2-(arilamino)-tiazol como se describió en el arte (Sharma, et al., Tetrahedron, 15: 53-59, 1961; Schantl, et al., Synth. Commun. 28:1451-1462, 1998).

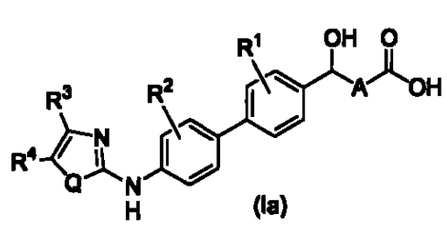
Los compuestos de Fórmula (VII) pueden prepararse a través de métodos conocidos en el arte, tales como los siguientes: (a) 2-cloro-5-cianobenzotiazol y 2-cloro-6-cianobenzotiazol (WO 2002000633); (b) 5-acetamido-2-clorobenzotiazol (Sharpe, et al., J. Med. Chem,15:523-529, 1972); (c) 6-acetamido-2-cloro-benzotiazol (Katz, J. Am. Chem. Soc. 73:4007-4010, 1951); (d) 2-cloro-5-benzotiazolcarboxamida, 2-cloro-N-metil-6-benzotiazolcarboxamida, 2-cloro-N-etil-5-benzotiazolcarboxamida, 2-cloro-N,N-dimetil-5-benzotiazolcarboxamida, 2-cloro-N,N-dimetil-6-benzotiazolcarboxamida, 2-cloro-N-(2-hidroxietil)-5-benzotiazol-carboxamida, 2-cloro-N-(2-hidroxietil)-6-benzotiazolcarboxamida, y 2-cloro-7-morfolinocarbonil-benzotiazol (Patente de los Estados Unidos No. 3.654.296); (e) 6-butoxi-2-cloro-benzotiazol (Bordi, et al., Farmaco 49: 153-166, 1994); (f) 2-cloro-6-isopropoxi-benzotiazol, 2-cloro-5-ciano-benzoxazol y 5-ciano-2-metiltiobenzotiazol (Sol. de Patente Europea EP1308439A1); (g) 2-cloro-5-metilsulfonil-benzoxazol (Lok, et al., J. Org. Chem. 61: 3289-3297, 1996); (h) 2-cloro-5-(4-metil-fenil)-tiazol, 2-cloro-5-(4-isopropil-fenil)-tiazol, y 2-cloro-5-(2,4-dimetil-fenil)-tiazol (Merljanian, et al., J. Org. Chem. 51: 543-545, 1986; (i) 2-cloro-5-(4-metoxi-fenil)-tiazol (Solicitud Francesa FR 2152345); (j) 2-cloro-4,5-dimetiltiazol (Begtrup, et al., Acta Chem.

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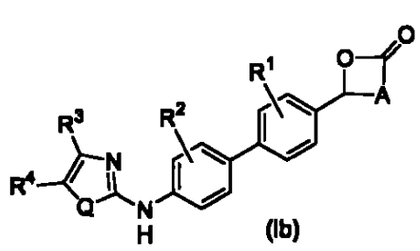
Scand. 46: 372-383, 1992); (k) 2-cloro-4-hidroximetiltiazol (WO 2000078746); (l) 2-cloro-4-metiltiazol (Sol. de Pat. Europea EP1216997); (m) 2-cloro-5-ciano-benzoxazol, 2-clorobencimidazol-5-carbonitrilo, 2-cloro-5-trifluorometilbencimidazol, 2-cloro-5-fluorobenzoimidazol, 2,5-diclorobenzoimidazol, 2-cloro-5-nitro-benzoimidazol, 2-cloro-1-metilbenzoimidazol, 2-cloro-5-trifluorometil-1-metil-benzoimidazol, y 2-cloro-5-fluoro-1-metilbenzoimidazol (Sol. de Pat. Europea EP1308439A1); (n) 2-cloro-1-metil-benzoimidazol, 2-cloro-1-etil-benzoimidazol, 2-cloro-1-isopropil-benzoimidazol, 2-cloro-1-bencil-benzoimidazol, y 2-cloro-6-fluoro-1-metil-1-benzoimidazol (WO 2001047898); (o) 2-cloro-1-ciclopropil-benzoimidazol (Orjales, et al., J. Med. Chem. 40: 586-593, 1997); (p) 2-cloro-7-metoxi-1-isopropil-benzoimidazol y 2-cloro-5-fluoro-1-isopropil-benzoimidazol (Solicitud Francesa FR 2773800).

Los compuestos que tienen la Fórmula (Ia) pueden prepararse a partir de los compuestos de Fórmula (I) o Fórmula (VI), mediante el uso de agentes reductores selectivos y métodos para la reducción selectiva conocidos por aquellos expertos en el arte. Por ejemplo, puede tratarse un compuesto de Fórmula (I) con borohidruro de sodio o un agente reductor similar para generar el correspondiente compuesto de Fórmula (Ia).

Los compuestos de Fórmula (Ib) se preparan a partir de compuestos de Fórmula (Ia) a través de métodos estándar para la lactonización de hidroxiácidos (por ej. en presencia de un catalizador ácido tal como TsOH) en un solvente anhidro tal como tolueno.



(Ia)



(Ib)

~~223~~
223

Pueden encontrarse ejemplos de la invención en los Ejemplos descritos a continuación y en las Tablas 1 y 2. Se pretende que los compuestos descritos en los Ejemplos sean representativos de la invención, y se comprenderá que el alcance de la invención no se limita con el alcance de los ejemplos. Aquellos expertos en el arte reconocerán que la invención puede practicarse con variaciones de las estructuras, los materiales, las composiciones y los métodos revelados, y dichas variaciones se consideran dentro del ámbito de la invención.

PREPARACIÓN DE LOS COMPUESTOS DE LA INVENCIÓN

Información General

Espectro de Masa

Los espectros de masa por ionización química (CI-MS) se obtuvieron con un espectrómetro de masa Hewlett Packard 5989A equipado con un Cromatógrafo Gaseoso Hewlett Packard 5890 con una columna J & W DB-5 (recubrimiento 0,25 uM; 30 m x 0,25 mm). La fuente de iones se mantuvo a 250°C y se barrieron los espectros desde 50-800 uma a 2 seg. por barrido.

Los datos de cromatografía líquida – espectros de masa por electroaspersión (CL-EM) se obtuvieron usando uno de los siguientes dos métodos. En los Ejemplos y las Tablas provistas a continuación, los datos de CL-EM se suministran con tiempos de retención (tiempo de ret.) de HPLC. Excepto donde se indique de otro modo, se usó el método 1.

Método 1: Hewlett-Packard 1100 HPLC equipado con un bombeador cuaternario, un detector de longitud de onda variable fijado a 254 nm, una columna YMC pro C-18 (2 x 23 mm, 120A), y un espectrómetro de masa con trampa de iones Finnigan LCQ con ionización por electroaspersión. Se barrieron los espectros desde 120-1200 uma usando un tiempo iónico variable de acuerdo con el número de iones en la fuente. Los eluyentes fueron: A: 2% de acetonitrilo en agua con 0,02% de TFA, y B: 2% de agua en acetonitrilo con 0,018% de TFA.

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Se usó elución con gradiente desde 10% de B hasta 95% de B durante 3,5 minutos a un caudal de flujo de 1,0 ml/min con una retención inicial de 0,5 minutos y una retención final de 0,5 minutos a 95% de B. El tiempo total del ciclo fue de 6,5 minutos.

Método 2: Sistema Gilson HPLC equipado con dos bombeadores Gilson 306, un Gilson 215 Autosampler, un detector con arreglo de diodos Gilson, una columna YMC Pro C-18 (2 x 23mm, 120 A), y un espectrómetro de masa con cuadrupolo simple Micromass LCZ con ionización por electroaspersión por z-spray. Se barrieron los espectros desde 120-800 uma durante 1,5 segundos. Se adquirieron, además, los datos de ELSD (Evaporative Light Scattering Detector - Detector de Difracción con Luz por Evaporación) como canal analógico. Los eluyentes fueron: A: 2% de acetonitrilo en agua con 0,02% de TFA, y B: 2% de agua en acetonitrilo con 0,018% de TFA. Se usó elución con gradiente desde 10% de B hasta 90% de B durante 3,5 minutos a un caudal de flujo de 1,5 ml/min con una retención inicial de 0,5 minutos y una retención final de 0,5 minutos a 90% de B. El tiempo total del ciclo fue de 4,8 minutos. Se usó un valor extra de conmutación para la conmutación y la regeneración de la columna.

Espectros de RMN

Se realizó espectrometría por 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 ID Wilmad para RMN de 5 mm RMN. Se obtuvieron los espectros a 293°K. Los desplazamientos químicos se registraron en la escala de ppm y se relacionaron con las señales de solvente 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

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225

DMSO-d_6, 1,3 ppm para CD_3CN, 49,0 ppm para CD_3OD, 53,8 ppm para CD_2Cl_2 y 77,0 ppm para $CDCl_3$ para espectros de ^{13}C.

Cromatografía Quiral

La cromatografía quiral se llevó a cabo usando Pirkle Covalent (R,R) Whelk-O 2 10/100 de Regis Technologies como fase fija. La fase móvil estaba formada por A = Hexano (que contenía 0,1% de TFA) y B = alcohol isopropílico (que contenía 0,1% de TFA). El gradiente usual fue 10% de B hasta 60% de B durante 25 minutos. En algunos casos, se usó un gradiente de 10 a 90% de B o 50 a 90% de B. La cuantificación y la recolección de fracciones se basó en la detección de UV a 330 nm (también a 280 nm). Normalmente se disolvieron las muestras en DMF antes de la inyección; para el trabajo analítico, estas soluciones de muestra se diluyeron en forma adicional con metanol. Para el trabajo analítico, se usaron una columna de 4,6 x 250 mm, caudal de flujo = 1 ml/min, y HPLC analítica de Shimadzu. Para el trabajo preparativo, se usaron una columna de 20 x 250 mm, caudal de flujo = 25 ml/min, y HPLC Gilson, con una cantidad de muestra inyectada típica de 50 mg.

Abreviaturas y Siglas

Cuando se usan las siguientes abreviaturas en toda la memoria descriptiva, éstas tienen el siguiente significado:

ac.	acuoso
BuOH	butanol
$CDCl_3$	cloroformo deuterado
Celite®	agente filtrante de tierra diatomácea, ®Celite Corp.
DCE	dicloroetano
DCM	diclorometano
DMF	*N,N*-dimetilformamida

~~220~~

226

DMSO	dimetil sulfóxido
DMSO-d_6	dimetil sulfóxido deuterado
ee	exceso enantiomérico
IE-EM	impacto electrónico - espectrometría de masa
IES-EM	ionización por electroaspersión - espectrometría de masa
EtOH	etanol
EtOAc	acetato de etilo
h	hora(s)
iPrOH	isopropanol
CG-EM	cromatografía gaseosa - espectrometría de masa
HPLC	cromatografía líquida de alta presión
HRMS	espectrometría de masa de alta resolución
CL-EM	cromatografía líquida - espectrometría de masa
MeI	yoduro de metilo
MeOH	metanol
min	minutos
EM	espectrometría de masa
RMN	resonancia magnética nuclear
$PdCl_2$(dppf)	1,1'-bis(difenilfosfina)ferrocen] dicloropaladio(II)
p.o.	administrado por vía oral
Rr	Factor de retención por TLC
ta	temperatura ambiente
TFA	ácido trifluoroacético
THF	tetrahidrofurano
TLC	cromatografía en placa delgada

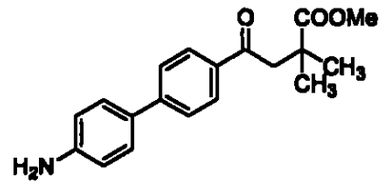
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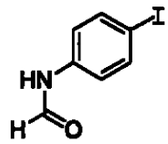
Preparación de los Compuestos de Fórmula (II), (V) y (VI)

Intermediario A

4-(4'-amino-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo



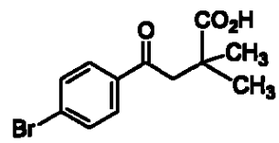
4-Yodoformanilida



Paso 1. A una solución de 4-yodoanilina (30,0 g, 137 mmol) en 100 ml de THF y 100 ml de tolueno, se agregó lentamente una solución de anhídrido acético (16,0 g, 157 mmol) y ácido fórmico (10,8 g, 235 mmol) a partir de un embudo de adición bajo atmósfera de argón. Se mantuvo la temperatura de la mezcla de reacción por debajo de 15°C durante el agregado. Luego de finalizar el agregado, se agitó la mezcla de reacción a t.a. hasta la mañana siguiente. Se diluyó la mezcla de reacción con agua (300 ml) y acetato de etilo (200 ml). Se separó la fase orgánica, se lavó con agua (2 x 200 ml), y 200 ml solución acuosa saturada de bicarbonato de sodio. Luego de secar sobre sulfato de sodio, se concentró la mezcla a presión reducida para producir 4-yodoformanilida como un sólido blancuzco (33,5 g, >98%). ^{1}H RMN (DMSO-d_6) δ 10,27 (s, 1H), 8,26 (d, J = 2 Hz, 1H), 7,64 (d, J = 12 Hz, 2H), 7,40 (d, J = 11,7 Hz, 2H) y 30% de tautómero; IES-EM *m/z* 248,0 (MH^+).

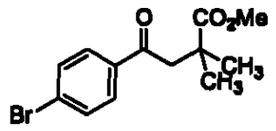
ácido 4-(4-Bromofenil)-2,2-dimetil-4-oxobutanoico

228
229



Paso 2. A una solución enfriada (baño de hielo/agua) de bromobenceno (7,71 g, 49,1 mmol) y 3,3-dimetildihidro-2,5-furandiona (5,99 g, 46,7 mmol) en dicloroetano (150 ml) se agregó tricloruro de aluminio (13,28 g, 99,58 mmol). Se retiró el baño de hielo y se agitó la mezcla de reacción a t.a. hasta la mañana siguiente. Se enfrió la mezcla nuevamente en un baño de hielo/ agua, y luego se desactivó con ácido clorhídrico acuoso 1M. Se agregó agua (70 ml) y se separaron las fases. Se extrajo la fase acuosa con acetato de etilo (3 x 50 ml). Se secaron las fases orgánicas combinadas sobre sulfato de magnesio anhidro y se concentraron a presión reducida. Se purificó el residuo por cromatografía flash (aparato Biotage, 17:83 acetato de etilo/hexano) para dar ácido 4-(4-bromofenil)-2,2-dimetil-4-oxobutanoico como un sólido blanco (8,34 g, 63%). CL-EM: tiempo de ret. 2,79 min; *m/z* 284,8 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,36 (s, 6H), 3,27 (s, 2H), 7,60 (d, 2H), 7,81 (d, 2H).

4-(4-bromofenil)-2,2-dimetil-4-oxobutanoato de metilo

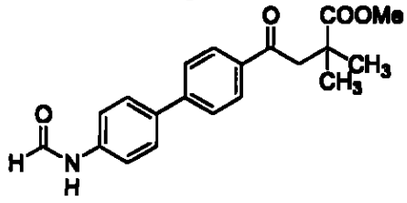


Paso 3. A una solución de ácido 4-(4-bromofenil)-2,2-dimetil-4-oxobutanoico (8,33 g, 29,2 mmol) y 2,2-dimetoxipropano (3,95 g, 37,9 mmol) en metanol (100 ml) se agregó HCl 1 M en dioxano (2,0 ml). Se agitó la mezcla de reacción a 50°C durante 22 h. Se concentró la mezcla a presión reducida. Se agregó tolueno (2 x 60 ml) y se concentró la

229

mezcla nuevamente (2x) para producir 4-(4-bromofenil)-2,2-dimetil-4-oxobutanoato de metilo como un semisólido blancuzco (8,60 g, 99%). Este material se usó en el paso siguiente sin purificación adicional. CL-EM: tiempo de ret. 3,23 min; *m/z* 298,8 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,34 (s, 6H), 3,28 (s, 2H), 3,67 (s, 3H), 7,58 (d, 2H), 7,78 (d, 2H).

4-[4'-(formilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoato de metilo

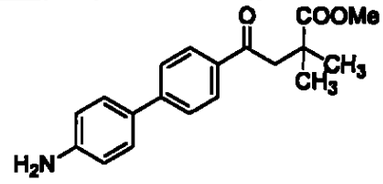


Paso 4. En un balón de tres bocas de 2 l, se colocaron 4-yodoformanilida (30,0 g, 121 mmol, 1,0 eq), bis(pinacolato)diboro (30,8 g, 121 mmol, 1,0 eq), acetato de paladio (0,82 g, 3,6 mmol, 3% en moles), acetato de potasio (35,70 g, 364,3 mmol), y 500 ml de *N,N*-dimetilformamida. Se eliminó el gas de la mezcla burbujeando argón suavemente a través de la solución durante 30 minutos a ta. Luego se calentó la mezcla a 80°C bajo argón hasta completar la reacción (2-3 horas). Luego de enfriar la mezcla hasta la ta, se agregaron 4-(4-bromofenil)-2,2-dimetil-4-oxobutanoato de metilo (36,3 g, 121 mmol), carbonato de cesio (59,4 g, 182 mmol), y tetrakistrifenilfosfin paladio (4,2 g, 3,6 mmol, 3 % en moles). Luego se calentó la mezcla de reacción a 80°C hasta la mañana siguiente bajo argón. Se enfrió la mezcla hasta la ta, y se diluyó lentamente con agua (1,5 L), lo que provocó la precipitación del material sólido. Se retiraron los sólidos por filtración, y se lavaron con 500 ml de agua. Luego se disolvieron los sólidos en 500 ml de cloruro de metileno, y se retiraron las partículas negras pasando la solución a través de un taco de Celite®. Se lavó el filtrado con 150 ml de agua (2x). Luego de secar la solución sobre sulfato de sodio, se concentró la solución a presión reducida para producir un residuo marrón, oscuro. Se agitó el residuo en acetato

230.

de etilo (200 ml) y hexano (200 ml) durante 1 h. Luego de filtrar y secar, se obtuvo 4-[4'-(formilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoato de metilo como un sólido amarillo (28,0 g, 68%). ^{1}H RMN ($CDCl_3$) δ 8,42 (d, *J* = 2 Hz, 1H), 7,98 (d, *J* = 8 Hz, 2H), 7,62 (m, 6H), 3,70 (s, 3H), 3,33 (s, 2H), 1,35 (s, 6H) y 40% de tautómero; IES-EM *m/z* 340,1 (MH^+).

4-(4'-amino-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo

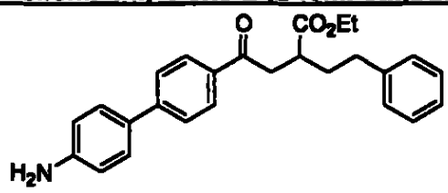


Paso 5. A una suspensión de 4-[4'-(formilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoato de metilo (2,40 g, 7,07 mmol) en 20 ml de metanol, se agregó 7 ml de ácido clorhídrico concentrado a temperatura inferior a la ta. Se agitó la mezcla de reacción a t.a. hasta la mañana siguiente. Se concentró la mezcla a presión reducida y solución acuosa saturada de bicarbonato de sodio se agregó lentamente hasta que el pH fue >8,0. Luego se extrajo la fase acuosa con cloruro de metileno (2 x 25 ml), y se secó la fase orgánica combinada sobre sulfato de sodio. Se concentró la mezcla a presión reducida para producir 4-(4'-amino-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo como un sólido rojo claro (2,1 g, 95%). ^{1}H RMN ($CDCl_3$) δ 7,96 (d, *J* = 9 Hz, 2H), 7,60 (d, *J* = 9 Hz, 2H), 7,46 (d, *J* = 9 Hz, 2H), 6,76 (d, *J* = 9 Hz, 2H), 3,85 (br s, 2H), 3,69 (s, 3H), 3,32 (s, 2H), 1,35 (s, 6H); IES-EM *m/z* 312,4 (MH^+); HRMS *m/z* calculado para MH^+ 312,1594, analítico 312,1597.

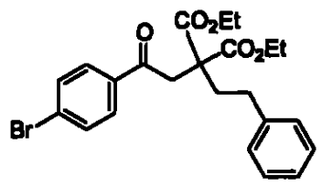
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Intermediario B

4-(4'-amino-1,1'-bifenil-4-il)-4-oxo-2-(2-fenil-etil)butanoato de etilo



2-[2-(4-bromofenil)-2-oxoetil]-2-(2-feniletil)-malonato de dietilo

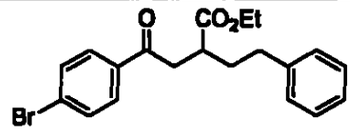


Paso 1. A un balón de 3 bocas de 500 ml equipado con entrada de argón y un embudo de incorporación, se agregó hidruro de sodio (95%, 1,40 g, 58,3 mmol) seguido de tetrahidrofurano (30 ml). Luego se enfrió la suspensión resultante hasta 0°C y se agregó 2-(2-feniletil)malonato de dietilo (14,0 g, 53,0 mmol) en tetrahidrofurano (20 ml) gota a gota durante 20 minutos. Se retiró el baño de frío y se dejó entibiar la mezcla de reacción hasta ta durante 45 minutos. Se agregó rápidamente una solución de 2-bromo-1-(4-bromofenil)-etanona (14,72 g, 58,26 mmol) en tetrahidrofurano (40 ml) y se agitó la mezcla rojo-anaranjada resultante a t.a. durante 16 h. Se vertió la mezcla cuidadosamente en 300 ml de ácido clorhídrico 1N, y se agitó la mezcla resultante durante 10 minutos y se extrajo dos veces con acetato de etilo. Se secaron los extractos combinados sobre sulfato de magnesio anhidro y se concentraron a presión reducida. Se purificó el residuo resultante por cromatografía flash (Biotage flash 75, 10:90 acetato de etilo/hexano) para producir 2-[2-(4-bromofenil)-2-oxoetil]-2-(2-feniletil)malonato de dietilo (14,8 g, 61%). Tiempo de retención de CL-EM 3,89 min, *m/z* 461,2 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,26 (t, 6H), 2,41-2,45 (m, 2H), 2,56-2,59 (m, 2H), 3,67 (s, 2H), 4,23 (q, 4H), 7,14-7,22 (m, 3H), 7,22 (d, 2H), 7,61 (d, 2H), 7,79 (d, 2H).

232

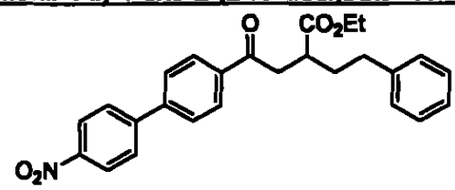
232

4-(4-bromofenil)-4-oxo-2-(2-feniletil)butanoato de etilo



Paso 2. A una solución de 2-[2-(4-bromofenil)-2-oxoetil]-2-(2-feniletil)malonato de dietilo (7,89 g, 17,1 mmol) en acetona (18,5 ml) y etanol (17,0 ml) se agregó solución acuosa 1N de hidróxido de sodio (17,1 ml), y se calentó la solución resultante a 50°C durante 3 h. Luego se eliminó el solvente a presión reducida a través de evaporación por rotación y se concentró adicionalmente el residuo resultante con alto vacío durante 1 h. Se disolvió el residuo nuevamente en dimetoxietano (18,5 ml) y se calentó la solución a 80°C durante 2,5 h. Se enfrió la mezcla hasta la ta, se diluyó con acetato de etilo, y se lavó con agua. Se secó la fase orgánica sobre sulfato de magnesio anhidro y se concentró con alto vacío. Se purificó el residuo resultante por cromatografía flash (Biotage flash 75, 10:90 acetato de etilo/hexano) para producir 4-(4-bromofenil)-4-oxo-2-(2-feniletil)butanoato de etilo (4,32 g, 65%). Tiempo de retención de CL-EM 3,79 min, *m/z* 389,2 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,20 (t, 3H), 1,78-1,94 (m, 2H), 2,62 (t, 2H), 2,86-3,01 (m, 2H), 3,26-3,36 (m, 1H), 4,10 (q, 2H), 7,05-7,11 (m, 3H), 7,18-7,23 (m, 2H), 7,51 (d, 2H), 7,72 (d, 2H).

4-(4'-nitro-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato de etilo

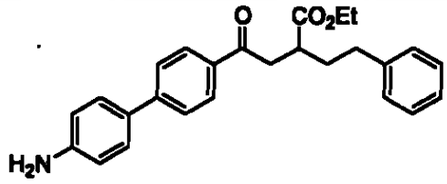


Paso 3. Se agregó 4-(4-bromofenil)-4-oxo-2-(2-feniletil)butanoato de etilo (4,32 g, 11,1 mmol) y ácido 4-nitrofenilborónico (2,22, 13,3 mmol) a un matraz seco bajo argón. Se agregaron tolueno (100 ml), dioxano (25 ml), carbonato de sodio acuoso saturado (30 ml), y [1,1'-bis(difenilfosfin)-ferrocen]dicloro paladio(II) (complejo 1:1 con diclorometano, 453 mg, 0,55 mmol) y se eliminó totalmente el

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233

gas a la mezcla. Luego se calentó la mezcla resultante a 85°C durante 16 h antes de enfriar hasta ta. Se agregó agua y se extrajo la mezcla dos veces con acetato de etilo. Se secaron los extractos combinados sobre sulfato de magnesio anhidro y se concentraron a presión reducida. Se purificó el residuo por cromatografía flash (Biotage flash 75, 5:1 acetato de etilo/hexano) para producir 4-(4'-nitro-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato de etilo (3,6 g, 75%). Tiempo de ret. de HPLC 3,99 min, ^{1}H RMN (300 MHz, $CDCl_3$) δ 1,29 (t, 3H), 1,85-2,08 (m, 2H), 2,71 (t, 2H), 3,05-3,20 (m, 2H), 3,45-3,52 (m, 1H), 4,20 (q, 2H), 7,18-7,31 (m, 5H), 7,72 (d, 2H), 7,78 (d, 2H), 8,05 (d, 2H), 8,33 (d, 2H).

4-(4'-amino-1,1'-bifenil-4-il)-4-oxo-2-(2-fenil-etil)butanoato de etilo



Paso 4. A una solución de 4-(4'-nitro-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato de etilo (5,35 g, 12,4 mmol) en etanol 85% (160 ml) se agregó polvo de hierro (6,94 g) seguido de una solución acuosa 2N de ácido clorhídrico (6,2 ml). Se reflujó la mezcla resultante durante 2,5 h, se filtró a través de un taco de Celite®, y se extrajo con acetato de etilo. Se secaron los extractos orgánicos combinados sobre sulfato de magnesio anhidro y se concentraron a presión reducida para producir 4-(4'-amino-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato de etilo (4,74 g, 95%). Tiempo de retención de CL-EM 3,22 min, *m/z* 402,0 (MH^+); ^{1}H RMN (300 MHz, $CDCl_3$) δ 1,18 (t, 3H), 1,83-2,10 (m, 2H), 2,65 (t, 2H), 3,03-3,12 (m, 2H), 3,41-3,48 (m, 1H), 4,12 (q, 2H), 6,70 (d, 2H), 7,19 (d, 4H), 7,25 (m, 1H), 7,38 (d, 2H), 7,53 (d, 2H), 7,89 (d, 2H).

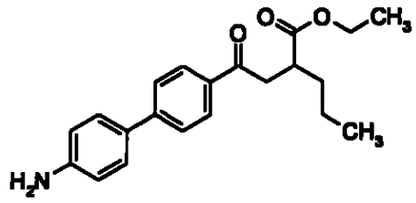
Este compuesto intermediario 4-(4'-amino-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato etilo, una mezcla racémica, se separó en sus dos

234
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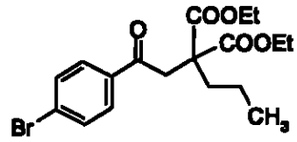
isómeros enantioméricos (*R*) y (*S*) por HPLC preparativa quiral usando una columna Pirkle Covalent (R,R) Whelk-O 2 10/100 (25 cm x 21,1 mm), y un gradiente para elución con solvente de 50% de isopropanol en hexano a 85% isopropanol en hexano, que contenía 0,1% de ácido trifluoroacético, a un caudal de flujo de 30 mL/min. El monitoreo por detección ultravioleta (254 nm) permitió la identificación y el aislamiento de las muestras enanito enriquecidas de los dos isómeros, que pudieron usarse para preparar los enantiómeros (*R*) y (*S*) individuales de los compuestos de la invención.

Intermediario C

2-[2-(4'-amino-1,1'-bifenil-4-il)-2-oxoetil]pentanoato de etilo



2-[2-(4-bromofenil)-2-oxoetil]-2-propilmalonato de dietilo



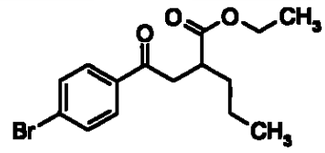
Paso 1. A un matraz de 3 bocas de 100 ml se agregó hidruro de sodio (95%, 0,55 g, 22 mmol) seguido de tetrahidrofurano (13 ml). Se enfrió la suspensión hasta 0°C, y se agregó gota a gota una solución de propilmalonato de dietilo (4,00 g, 19,8 mmol) en tetrahidrofurano (10 ml) durante 10 minutos. Se retiró el baño de frío y se dejó entibiar la mezcla de reacción hasta ta durante 45 minutos. De agregó una solución de 2,4'-bromoacetofenona (5,50 g, 19,8 mmol) en tetrahidrofurano (30 ml) a través de un embudo de adición durante 10 minutos, y se agitó la mezcla de reacción rojo anaranjado resultante a t.a. durante 16 h. Se vertió

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235

lentamente la mezcla de reacción en solución acuosa 1,0 N de ácido clorhídrico (100 ml), se enfrió a 0°C, se agitó durante 15 minutos, seguido del agregado de acetato de etilo (100 ml) y agua (100 ml), y se separaron las fases. Se extrajo la fase acuosa con acetato de etilo adicional (75 ml), se lavaron las fases orgánicas combinadas con solución saturada acuosa de cloruro de sodio (75 ml), se secaron sobre sulfato de magnesio anhidro, se filtraron *al vacío* a través de 2,5 cm de Celite®/2,5 cm de sílice, y se concentró el filtrado a presión reducida, para producir 2-[2-(4-bromofenil)-2-oxoetil]-2-propilmalonato de dietilo (7,62 g, 86%). Tiempo de retención de CL-EM 3,74 min, *m/z* 399,0 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 0,82-0,98 (m, 3H), 1,10-1,45 (m, 8 H), 2,01-2,12 (m, 2H), 3,60 (s, 2H), 4,10-4,30 (m, 4H), 7,60 (d, 2H), 7,85 (d, 2H).

2-[2-(4-bromofenil)-2-oxoetil]pentanoato de etilo

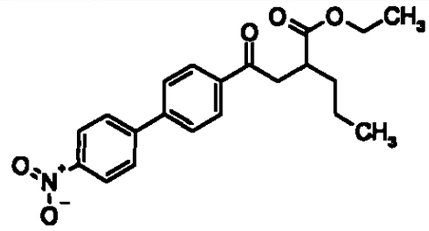


Paso 2. A un matraz de 200 ml se agregó 2-[2-(4-bromofenil)-2-oxoetil]-2-propilmalonato en bruto (7,62 g, 19,2 mmol), acetona (21 ml), y etanol (19 ml), seguido del agregado de solución acuosa 1N de hidróxido de sodio (19,1 ml). Se calentó la mezcla de reacción hasta 55°C durante 3 h. Luego se concentró la mezcla de reacción translúcida rojo anaranjada a presión reducida y se disolvió el residuo nuevamente en dimetoxietano (30 ml). Se calentó la mezcla hasta 80°C durante 3 h. Se enfrió la mezcla de reacción hasta ta, se diluyó con acetato de etilo (100 ml) y agua (100 ml), y se agitó durante 15 minutos hasta que casi todo el color se extrajo en la fase orgánica. Se separaron las fases y se extrajo la fase acuosa con acetato de etilo adicional (75 ml). Se lavaron las fases orgánicas combinadas con solución saturada acuosa de cloruro de sodio (75

~~236~~
236

ml), se secaron sobre sulfato de magnesio anhidro, y se concentraron a presión reducida para producir un aceite naranja. Se purificó el producto en bruto por cromatografía flash (10:1 hexano:acetato de etilo) para producir 2-[2-(4-bromofenil)-2-oxoetil]pentanoato de etilo (1,33 g, 20%). Tiempo de retención de CL-EM 3,60 min, *m/z* 326,05 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 0,87 (t, 3H), 1,25 (t, 3H), 1,29-1,43 (m, 2H), 1,57-1,73 (m, 2H), 2,90-3,08 (m, 2H), 3,34-3,47 (m, 2H), 4,15 (q, 2H), 7,59 (d, 4H), 7,82 (d, 2H).

2-[2-(4'-nitro-1,1'-bifenil-4-il)-2-oxoetil]pentanoato de etilo

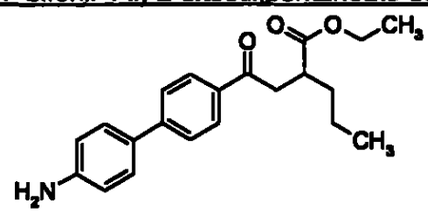


[096] Paso 3. a un matraz de 3 bocas de 150 ml provisto de un refrigerante a reflujo se agregó 2-[2-(4-bromofenil)-2-oxoetil]pentanoato de etilo (1,33 g, 4,10 mmol) y ácido 4-nitrofenil borónico (0,81 g, 4,9 mmol), se disolvió en tolueno (37 ml) y dioxano (10 ml), seguido del agregado de carbonato de sodio acuoso saturado (11 ml). Se insertó una aguja de calibre delgado en la mezcla bifásica y se eliminó el gas de la mezcla con argón durante 30 minutos, momento en el cual se agregó 1,2-bis[(difenilfosfin) ferroceno] dicloropaladio(II) (0,17 g, 0,20 mmol), seguido de 15 minutos de eliminación de gases. Se calentó la mezcla hasta 85°C durante 16 h. Se dejó enfriar la mezcla de reacción de color muy oscuro, y se diluyó con acetato de etilo (100 ml) y solución saturada acuosa de cloruro de sodio (100 ml). Se separaron las fases, se extrajo la fase acuosa dos veces con acetato de etilo (50 ml), y se lavaron las fases orgánicas combinadas con solución saturada acuosa de cloruro de

237.
237

sodio (75 ml), se secaron sobre sulfato de magnesio anhidro, y se filtraron *al vacío* a través de 2 cm de Celite®/2 cm de sílice. Se concentró el filtrado a presión reducida, dejando un aceite marrón rojizo oscuro, que se purificó por cromatografía flash (10:1 hexano:acetato de etilo, luego 7:1 hexano:acetato de etilo, luego 4:1 hexano:acetato de etilo) para producir 2-[2-(4'-nitro-1,1'-bifenil-4-il)-2-oxoetil]pentanoato de etilo (0,71 g , 48%). Tiempo de retención de CL-EM 3,88 min, *m/z* 369,8 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 0,95 (t, 3H), 1,30 (t, 3H), 1,35-1,50 (m, 2H), 1,60-1,83 (m, 2H), 3,0-3,18 (m, 2H), 3,5 (dd, 1H), 4,20 (q, 2H), 7,65-7,88 (d superpuesto, 4H), 8,10 (d, 2H), 8,35 (d, 2H).

2-[2-(4'-amino-1,1'-bifenil-4-il)-2-oxoetil]pentanoato de etilo



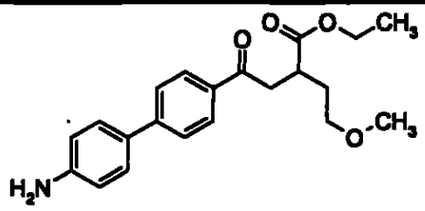
Paso 4. A un matraz de 100 ml provisto de un refrigerante a reflujo se agregó 2-[2-(4'-nitro-1,1'-bifenil-4-il)-2-oxoetil]pentanoato de etilo (0,71 g, 1,9 mmol) disuelto en etanol acuoso al 85% (24 ml), seguido del agregado de solución acuosa 2N de ácido clorhídrico (0,95 ml) y hierro finamente pulverizado (0) (1,10 g, 19,1 mmol), y se calentó la mezcla de reacción a 85°C durante 2 h. Luego de enfriar, se filtró la mezcla de reacción de color oscuro *al vacío* a través de 2 cm de Celite®/2 cm de sílice, logrando la eliminación de la totalidad de las partículas de hierro/ material basal. Se filtró el concentrado amarillo a presión reducida, generando un sólido que se trituró en 20 ml de dietil éter/20 ml de hexano, produciendo 2-[2-(4'-amino-1,1'-bifenil-4-il)-2-oxoetil]pentanoato de metilo como un sólido tostado (0,56 g, 88%).

238
238

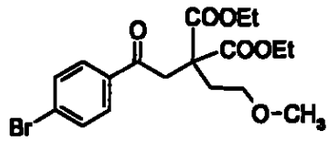
Tiempo de retención de CL-EM 2,82 min, *m/z* 340,4 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 0,87 (t, 3H), 1,13 (t, 3H), 1,25-1,40 (m, 2H), 1,44-1,64 (m, 2H), 2,78-2,90 (m, 1H), 3,06-3,40 (m, 2H), 3,95-4,10 (m, 2H), 5,30-5,64 (br s, 1H), 6,65 (d, 2H), 7,46 (d, 2H), 7,67 (d, 2H), 7,93 (d, 2H).

Intermediario D

4-(4'-amino-1,1'-bifenil-4-il)-2-(2-metoxietil)-4-oxobutanoato de etilo



2-[2-(4-bromofenil)-2-oxoetil]-2-(2-metoxietil)malonato de dietilo

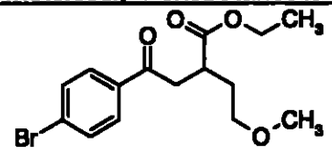


Paso 1. En un matraz de 100 ml se agregó hidruro de sodio (95%, 0,25 g, 10,1 mmol) seguido de tetrahidrofurano (5 ml). Se enfrió la suspensión hasta 0°C, y se agregó una solución de (2-metoxietil)-malonato de dietilo (2,0 g, 9,16 mmol) en tetrahidrofurano (10 ml) gota a gota durante 10 minutos. Se retiró el baño refrigerante y se dejó entibiar la mezcla de reacción hasta ta durante 45 minutos. Se agregó una solución de 2,4'-bromoacetofenona (2,55 g, 19,6 mmol) en tetrahidrofurano (15 ml) a través de un embudo de adición durante 10 minutos, y se agitó la mezcla de reacción resultante de color rojo anaranjado a t.a. durante 16 h. Se vertió lentamente la mezcla de reacción en solución acuosa 1N de ácido clorhídrico (50 ml) con enfriamiento a 0°C, y se agitó durante 15 minutos. Se agregaron acetato de etilo (75 ml) y agua (75 ml), y se separaron las fases. Se extrajo la fase acuosa con acetato de etilo adicional (50 ml), y se lavaron las fases orgánicas combinadas con

239
239

solución saturada acuosa de cloruro de sodio (75 ml), se secaron sobre sulfato de magnesio anhidro, se filtraron, y se concentraron el filtrado *al vacío* para producir 3,7 g de un aceite naranja. Este aceite se purificó por cromatografía flash (10:1 hexano/acetato de etilo, luego 4:1 hexano/acetato de etilo) para producir dietilo 2-[2-(4-bromofenil)-2-oxoetil]-2-(2-metoxietil)malonato (1,59 g, 42%). Tiempo de retención de CL-EM 3,40 min, *m/z* 415 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,20 (t, 6H), 2,38 (t, 2H), 3,09 (s, 3H), 3,40 (t, 2H), 3,74 (s, 2H), 4,19 (q, 4H), 7,60 (d, 2H), 7,83 (d, 2H).

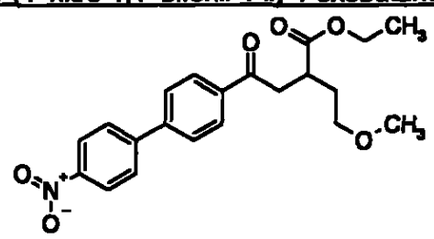
4-(4-bromofenil)-2-(2-metoxietil)-4-oxobutanoato de etilo



Paso 2. A un matraz de 150 ml se agregó 2-[2-(4-bromofenil)-2-oxoetil]-2-(2-metoxietil)malonato de dietilo (1,59 g, 3,59 mmol) disuelto en acetona (16 ml) y etanol (16 ml), seguido del agregado de solución 1N acuosa de hidróxido de sodio (3,6 ml). Luego se calentó la mezcla de reacción a 55°C durante 3 h. Se concentró la mezcla de reacción *al vacío* para eliminar los solventes, se disolvió nuevamente el residuo en dimetoxietano (32 ml), y se calentó la mezcla de reacción 80°C durante 3 h. Se enfrió la mezcla de reacción hasta ta, se diluyó con acetato de etilo (50 ml) y agua (50 ml), y se agitó durante 15 minutos hasta que casi todo el color se extrajo en la fase orgánica. Se separaron las fases, se extrajo la fase acuosa con acetato de etilo adicional (50 ml), y se lavaron las fases orgánicas combinadas con solución saturada acuosa de cloruro de sodio (50 ml), se secaron sobre sulfato de magnesio anhidro, y se concentraron *al vacío*, para producir 4-(4-bromofenil)-2-(2-metoxietil)-4-oxobutanoato de etilo (1,06 g, 86%). No se requirió

purificación adicional de este material. Tiempo de retención de CL-EM 3,18 min, *m/z* 342,8 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,35 (t, 3H), 1,77-1,92 (m, 1H), 1,94-2,10 (m, 1H), 3,05-3,2 (m, 2H), 3,35-3,50 (m, 3H), 4,09-4,25 (m, 2H), 7,60 (d, 2H), 7,83 (d, 2H).

2-(2-metoxietil)-4-(4'-nitro-1,1'-bifenil-4-il)-4-oxobutanoato de etilo

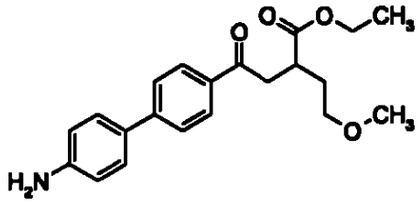


Paso 3. A un matraz de 3 bocas de 150 ml provisto de un refrigerante a reflujo se agregó 4-(4-bromofenil)-2-(2-metoxietil)-4-oxobutanoato etilo (1,06 g, 3,09 mmol) y ácido 4-nitro-fenil borónico (0,62 g, 3,70 mmol) disuelto en tolueno (30 ml) y dioxano (8,50 ml), seguido del agregado de solución saturada de carbonato de sodio (8,50 ml). Se insertó una aguja de calibre delgado en la mezcla bifásica y se eliminó el gas con argón durante 30 minutos, momento en el cual se agregó 1,2-bis[(difenilfosfina)ferroceno]dicloropaladio(II) (0,13 g, 0,15 mmol), seguido de un adicional de 15 minutos de eliminación de gases. Se calentó la mezcla de reacción a 85°C durante 16 h, y luego se dejó enfriar la mezcla de reacción resultante de color oscuro, y se diluyó con acetato de etilo (75 ml) y solución saturada acuosa de cloruro de sodio (75 ml). Se separaron las fases, se extrajo la fase acuosa dos veces con acetato de etilo (50 ml), y se lavaron las fases orgánicas combinadas con solución saturada acuosa de cloruro de sodio (75 ml), se secaron sobre sulfato de magnesio anhidro, y se filtraron *al vacío* a través de 2 cm de Celite®/2 cm de sílice. Se concentró el filtrado *al vacío*, dejando un aceite marrón rojizo oscuro, que se purificó por cromatografía flash

241

(hexano/acetato de etilo 4:1, luego hexano/acetato de etilo 3:1, luego hexano/acetato de etilo 2:1) para producir 2-(2-metoxietil)-4-(4'-nitro-1,1'-bifenil-4-il)-4-oxobutanoato de etilo (1,04 g ,88%). Tiempo de retención de CL-EM 3,38 min, *m/z* 385,9 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,27 (t, 3H), 1,80-1,95 (m, 1H), 1,95-2,10 (m, 1H), 3,10-3,25 (m, 2H), 3,40-3,58 (m, 3H), 4,17 (q, 2H), 7,67-7,82 (2d, 4H), 8,10 (d, 2H), 8,33 (d, 2H).

4-(4'-amino-1,1'-bifenil-4-il)-2-(2-metoxietil)-4-oxobutanoato de etilo

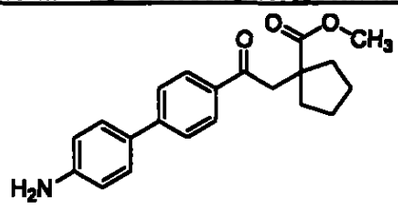


Paso 4. A un matraz de 100 ml provisto de un refrigerante a reflujo se agregó 2-(2-metoxietil)-4-(4'-nitro-1,1'-bifenil-4-il)-4-oxobutanoato de etilo (1,04 g, 2,71 mmol) disuelto en etanol acuoso al 85% (24 ml), seguido del agregado de solución acuosa 2N de ácido clorhídrico (1,35 ml) y hierro finamente pulverizado (0) (1,51 g, 27,1 mmol), y se calentó la mezcla de reacción a 85°C durante 2 h. Luego de enfriar, se filtró la mezcla de reacción de color oscuro *al vacío* a través de 2 cm de Celite®/2 cm de sílice, produciendo la eliminación de la totalidad de partículas de hierro y material polar. Se filtró el concentrado amarillo *al vacío*, generando un sólido que se purificó por cromatografía flash (hexano/acetato de etilo 3:1) produciendo 4-(4'-amino-1,1'-bifenil-4-il)-2-(2-metoxietil)-4-oxobutanoato de etilo como un sólido tostado (0,89 g, 93%). Tiempo de retención de CL-EM 2,33 min, *m/z* 356,2 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,18-1,33 (m, 3H), 1,79-2,10 (m superpuesto, 2H), 3,10-3,21 (m, 2H), 3,30 (s, 3H), 3,48 (t, 3H), 4,16 (t, 3H), 7,15 (d, 2H), 7,55 (d, 2H), 7,62 (d, 2H), 8,03 (d, 2H).

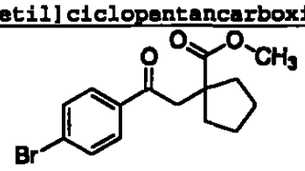
242
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Intermediario E

1-[2-(4'-amino-1,1'-bifenil-4-il)-2-oxoetil]ciclopentancarboxilato de metilo



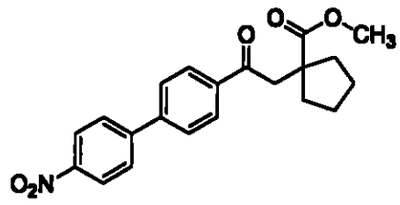
1-[2-(4-bromofenil)-2-oxoetil]ciclopentancarboxilato de metilo



Paso 1. A un matraz de 150 ml se agregó diclorometano (70 ml), 1-(2-cloro-2-oxoetil)ciclopentancarboxilato de metilo (3,50 g, 16,8 mmol) [preparado como se describe en Bajaj, et al., J. Indian Chem. Soc. 52: 1076-78, 1975] y bromobenceno (2,77 g, 17,6 mmol), y se enfrió la mezcla de reacción hasta 0°C antes de agregar lentamente tricloruro de aluminio (4,77 g, 35,7 mmol). Se agitó la mezcla durante 1 h a 0°C, luego durante 12 h a ta. Se vertió lentamente la mezcla de reacción en 50 ml de (0°C) solución acuosa 1N de ácido clorhídrico fría. Se agregó agua (50 ml), seguido de acetato de etilo (100 ml), y se agitó la mezcla de reacción 30 minutos. Se separaron las fases y se extrajo la fase acuosa con acetato de etilo adicional (100 ml). Se lavó la fase orgánica combinada con cloruro de sodio acuoso saturado (100 ml), se secó sobre sulfato de magnesio anhidro, y se concentró a presión reducida para producir un aceite marrón que se purificó por cromatografía flash (10:1/hexano: acetato de etilo) para producir 1-[2-(4-bromofenil)-2-oxoetil]ciclopentancarboxilato de metilo como un sólido cristalino amarillo (1,62 g, 30%). Tiempo de retención de CL-EM 3,45 min, m/z 324,8 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,50-1,83 (señales superpuestas, 6H),

2,22-2,33 (m, 2H), 3,37 (s, 2H), 3,66 (s, 3H), 7,59 (d, 2H), 7,80 (d, 2H).

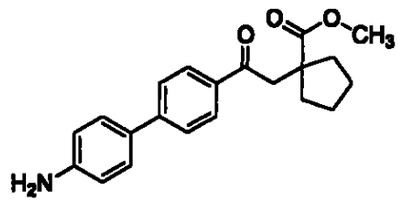
1-[2-(4'-nitro-1,1'-bifenil-4-il)-2-oxoetil]ciclopentancarboxilato de metilo



Paso 2. A un matraz de 3 bocas de 150 ml provisto de un refrigerante a reflujo se agregó 1-[2-(4-bromofenil)-2-oxoetil]ciclopentancarboxilato de metilo (1,58 g, 4,64 mmol), ácido 4-nitrofenil borónico (0,93 g, 5,6 mmol), tolueno (45 ml), y dioxano (13 ml), seguido del agregado de una solución acuosa saturada de carbonato de sodio (13 ml). Se eliminó el gas de la mezcla usando argón y se agregó 1,2-bis[(difenilfosfin) ferroceno] dicloropaladio(II) (0,19 g, 0,23 mmol), seguido de un adicional de 15 minutos de eliminación de gases, y se calentó la mezcla de reacción rojo oscuro hasta 85°C durante 16 h. Se dejó enfriar la mezcla de reacción de color muy oscuro, y luego se diluyó con acetato de etilo (100 ml) y solución saturada acuosa de cloruro de sodio (100 ml). Se separaron las fases y se extrajo la fase acuosa dos veces con acetato de etilo (50 ml). Se lavó la fase orgánica combinada con solución saturada acuosa de cloruro de sodio (100 ml), se secó sobre sulfato de magnesio anhidro, y se filtró a presión reducida a través de 2 cm de Celite®/2 cm de sílice. Se concentró el filtrado a presión reducida, dejando un aceite marrón rojizo oscuro, que se purificó por cromatografía flash (hexano/acetato de etilo 4:1, luego hexano/acetato de etilo 3:1, luego hexano/ acetato de etilo 2:1) para producir 1-[2-(4'-nitro-1,1'-bifenil-4-il)-2-

oxoetil]ciclopentancarboxilato de metilo (1,65 g, 93%). Tiempo de retención de CL-EM 3,56 min, *m/z* 368,0 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,56-1,85 (señales superpuestas, 6H), 2,23-2,37 (m, 2H), 3,45 (s, 2H), 3,67 (s, 3H), 7,70 (d, 2H), 7,77 (d, 2H), 8,06 (d, 2H), 8,34 (d, 2H).

1-[2-(4'-amino-1,1'-bifenil-4-il)-2-oxoetil]ciclopentancarboxilato de metilo

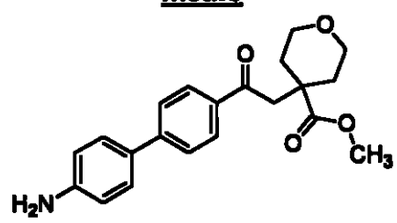


Paso 3. A un matraz de 100 ml provisto de un refrigerante a reflujo se agregó 1-[2-(4'-nitro-1,1'-bifenil-4-il)-2-oxoetil]ciclopentancarboxilato de metilo (1,68 g, 4,40 mmol) disuelto en etanol acuoso al 85% (55 ml), seguido del agregado de solución acuosa 2N de ácido clorhídrico (2,20 ml) y hierro finamente pulverizado (0) (2,46 g, 44,1 mmol). Se calentó la mezcla de reacción hasta 85°C durante 2 h. Luego de enfriar, se filtró la mezcla de reacción de color oscuro a presión reducida a través de 2 cm de Celite®/2 cm de sílice, para eliminar las partículas de hierro y las impurezas polares. Se filtró el concentrado amarillo a presión reducida, generando un sólido que se trituró con 20 ml de dietil éter/20 ml de hexano para producir 1-[2-(4'-amino-1,1'-bifenil-4-il)-2-oxoetil] ciclopentan-carboxilato de metilo como un sólido tostado claro (1,20 g, 76%). Tiempo de retención de CL-EM 2,71 min, *m/z* 338,1 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,55-1,84 (señales superpuestas, 6H), 2,25-2,35 (m, 2 H), 3,44 (s, 2H), 3,67 (s, 3H), 7,40-8,10 (señales superpuestas, 8H).

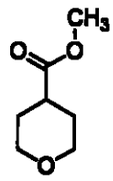
Intermediario F

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4-[2-(4'-amino-1,1'-bifenil-4-il)-2-oxoetil]tetrahidro-2H-piran-4-carboxilato de metilo

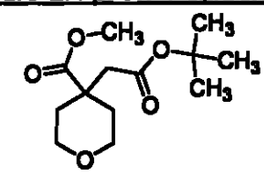


Tetrahidro-2H-piran-4-carboxilato de metilo



Paso 1. Se agregó ácido tetrahidro-2H-piran-4-carboxílico (1,00 g, 7,68 mmol) lentamente a una suspensión agitada de carbonato de potasio anhidro (1,17 g, 8,45 mmol) en acetona (40 ml), seguido de dimetil sulfato (0,8 ml, 8,45 mmol). Se agitó la mezcla y se calentó durante 3 h. Luego se eliminaron las sales inorgánicas por filtración y se lavaron con acetona, y se secó el filtrado y se concentró para dar tetrahidro-2H-piran-4-carboxilato de metilo (1,1 g, 99%), que se usó en el paso siguiente sin purificación adicional. CG-EM *m/z* 145 (MH^+); ^{1}H RMN (300 MHz, $CDCl_3$) δ 11,70-1,80 (m, 4H), 2,47-2,52 (m, 1H), 3,34-3,43 (m, 2H), 3,65 (s, 3H), 3,88-3,95 (m, 2H).

4-(2-*ter*-butoxi-2-oxoetil)tetrahidro-2H-piran-4-carboxilato de metilo

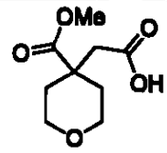


Paso 2. Se diluyó diisopropilamina (1,28 ml, 9,16 mmol) con tetrahidrofurano (2 ml) y se enfrió hasta -78°C. Se agregó gota a gota *n*-butil litio (2,5 M, 3,66 ml, 9,16 mmol), y se dejó agitar la solución durante 1 h. Se agregó tetrahidro-2H-piran-4-carboxilato de metilo (1,1 g, 7,63 mmol) en forma de solución en tetrahidrofurano

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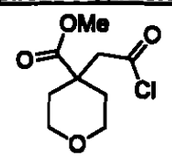
(1,5 ml) a -78°C. Se dejó entibiar la mezcla hasta -35°C y se agitó durante 1 h. Se agregó bromoacetato de *ter*-butilo (1,58 ml, 10,7 mmol) puro a -35°C. Se dejó entibiar la mezcla hasta 0°C y se agitó durante 2 h. Se agitó la mezcla a t.a. hasta la mañana siguiente. Se agregó agua a 0°C y se extrajo la mezcla con acetato de etilo. Se lavó la fase orgánica con salmuera, y se secó sobre sulfato de sodio. Se purificó el producto en bruto por cromatografía flash (Biotage Flash 40M, hexano/acetato de etilo 6:1) para producir 4-(2-*ter*-butoxi-2-oxoetil)tetrahidro-2H-piran-4-carboxilato de metilo (1,12 g, 56%). Tiempo de retención de CL-EM 2,47 min, *m/z* 258,7 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,38 (s, 9H), 1,52-1,61 (m, 2H), 2,00-2,07 (m, 2H), 2,50 (s, 2H), 3,52-3,60 (m, 2H), 3,70 (s, 3H), 3,71-3,77 (m, 2H).

Ácido [4-(metoxicarbonil)tetrahidro-2H-piran-4-il]acético



Paso 3. A una solución de 4-(2-ter-butoxi-2-oxoetil)tetrahidro-2H-piran-4-carboxilato de metilo (1,1 g, 4,26 mmol) en diclorometano (5,0 ml) se agregó ácido trifluoroacético (5,0 ml) y se agitó la solución resultante a t.a. durante 5 h. Se concentró la mezcla a presión reducida para producir ácido [4-(metoxicarbonil)-tetrahidro-2H-piran-4-il]acético (900 mg, 94%), que se usó en el paso siguiente sin purificación adicional. Tiempo de retención de CL-EM 0,93 min, *m/z* 202,9 (MH^+); ^1H RMN (300 MHz, DMSO-d_6) δ 1,60-1,70 (m, 2H), 2,10-2,15 (m, 2H), 2,68 (s, 2H), 3,62-3,71 (m, 2H), 3,72 (s, 3H), 3,79-3,86 (m, 2H).

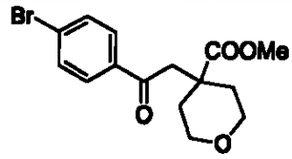
4-(2-cloro-2-oxoetil)tetrahidro-2H-piran-4-carboxilato de metilo



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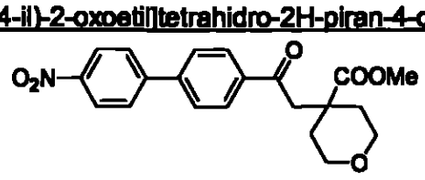
Paso 4. Se agregó cloruro de tionilo (20 ml) al ácido [4-(metoxicarbonil)-tetrahidro-2H-piran-4-il]acético (970 mg, 4,80 mmol) y se agitó la solución a t.a. durante 3 h. Luego se eliminó el solvente y la mezcla se hizo azeotrópica con dicloroetano tres veces para producir 4-(2-cloro-2-oxoetil)tetrahidro-2H-piran-4-carboxilato de metilo (1,05 g, 99%), que se utilizó sin purificación en el paso siguiente.

4-[2-(4-bromofenil)-2-oxoetil]tetrahidro-2H-piran-4-carboxilato de metilo



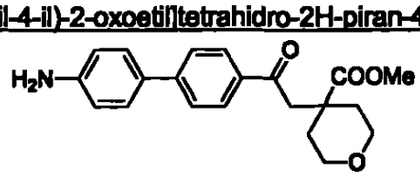
Paso 5. A una solución de 4-(2-cloro-2-oxoetil)tetrahidro-2H-piran-4-carboxilato de metilo (1,06 g, 4,8 mmol) y bromobenceno (1,13 g, 7,21 mmol) en diclorometano (20 ml) a 0°C se agregó cloruro de aluminio (1,92 g, 14,4 mmol). Se eliminó el baño de hielo-agua y se agitó la mezcla de reacción a t.a. durante 16 h. Luego se enfrió la mezcla a 0°C y se desactivó con el agregado de solución 1 N de HCl y agua. Se extrajo la mezcla con diclorometano, y se secaron las fases orgánicas combinadas sobre sulfato de sodio. Luego se purificó el material en bruto por cromatografía flash (Biotage Flash 40 M, hexano/acetato de etilo 2:1, para producir 4-[2-(4-bromofenil)-2-oxoetil]tetrahidro-2H-piran-4-carboxilato de metilo (900 mg, 55%). Tiempo de retención de CL-EM 2,76 min; *m/z* 342,9 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,58-1,69 (m,. 2H), 2,12-2,18 (m, 2H), 3,28 (s, 2H), 3,64 (s, 3H), 3,69-3,77 (m, 4H), 7,59 (d, 2H), 7,77 (d, 2H).

4-[2-(4'-nitro-1,1'-bifenil-4-il)-2-oxoetil]tetrahidro-2H-piran-4-carboxilato de metilo



Paso 6. Se combinaron 4-[2-(4-bromofenil)-2-oxoetil]tetrahidro-2H-piran-4-carboxilato de metilo (820 mg, 2,40 mmol) y ácido 4-nitrofenil borónico (481 mg, 2,88 mmol) en un matraz seco bajo argón. Se agregaron tolueno (20 ml) y dioxano (5 ml), y se eliminó el gas de la solución resultante durante 30 minutos con una corriente de argón. Se continuó con la eliminación de gases durante el agregado de carbonato de sodio acuoso saturado (6 ml) y [1,1'-bis(difenilfosfina)-ferroceno]dicloro paladio(II), complejo 1:1 con diclorometano (98 mg, 0,12 mmol). Luego se calentó la mezcla resultante a 85°C durante 16 h antes de enfriar hasta ta. Se agregó agua, y se extrajo la fase acuosa dos veces con acetato de etilo. Luego se secaron las fases orgánicas combinadas sobre sulfato de magnesio anhidro y se concentraron a presión reducida. Se purificó el residuo resultante por cromatografía flash (Biotage Flash 40) usando acetato de etilo/hexano 1:1 para producir 4-[2-(4'-nitro-1,1'-bifenil-4-il)-2-oxoetil]tetrahidro-2H-piran-4-carboxilato de metilo (730 mg, 79%). Tiempo de retención de CL-EM 3,03; m/z 383,9 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,65-1,73 (m, 2H), 2,17-2,21 (m, 2H), 3,37 (s, 2H), 3,68 (s, 3H), 3,71-3,78 (m, 4H), 7,70 (d, 2H), 7,77 (d, 2H), 8,02 (d, 2H), 8,31 (d, 2H).

4-[2-(4'-amino-1,1'-bifenil-4-il)-2-oxoetil]tetrahidro-2H-piran-4-carboxilato de metilo



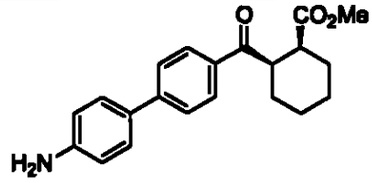
Paso 7. A una solución de 4-[2-(4'-nitro-1,1'-bifenil-4-il)-2-oxoetil]tetrahidro-2H-piran-4-carboxilato de metilo (1,24 g, 3,25 mmol) en etanol al 85% (50 ml) se agregó polvo de hierro (1,81 g), seguido de HCl acuoso 2 N (1,62 ml), y se reflujó la mezcla resultante durante 2,5 h. Luego se filtró la mezcla a través de un taco de Celite® y se extrajo el filtrado con diclorometano. Luego se secaron las fases orgánicas

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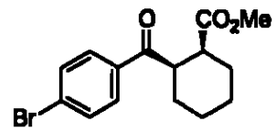
combinadas sobre sulfato de magnesio anhidro y se concentraron *al vacío* para producir 4-[2-(4'-amino-1,1'-bifenil-4-il)-2-oxoetil]tetrahidro-2H-piran-4-carboxilato de metilo (1,05 g, 91%). Tiempo de retención de CL-EM 2,20; *m/z* 354,0 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,57-1,66 (m, 2H), 2,09 (m, 2H), 3,28 (s, 2H), 3,61 (s, 3H), 3,64-3,71 (m, 4H), 6,76 (d, 2H), 7,42 (d, 2H), 7,54 (d, 2H), 7,88 (d, 2H).

Intermediario G

***cis*-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclohexancarboxilato de metilo**



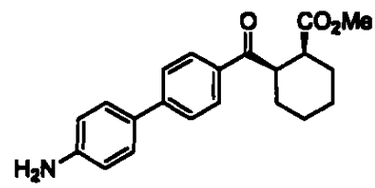
cis-2-(4-bromobenzoil)ciclohexancarboxilato de metilo



Paso 1. A una solución de ácido *cis*-2-(4-bromobenzoil)-1-ciclohexan-carboxílico (4,0 g, 12,85 mmol) en MeOH (50 ml) se agregó 2,2-dimetoxipropano (2,01 g, 19,28 mmol) y HCl (4,0 M en dioxano, 1,20 ml). Se agitó la solución resultante a 40°C durante 3 días, y luego se evaporó hasta la sequedad. Se purificó el residuo resultante por cromatografía flash (Biotage Flash 40M) usando 3 a 6% de acetato de etilo en hexanos para producir *cis*-2-(4-bromobenzoil)-ciclohexancarboxilato de metilo (1,76 g, 42%). Tiempo de retención de CL-EM 3,40; *m/z* 326 (MH^+); ^1H RMN (400 MHz, CD_2Cl_2) δ 1,35-1,51 (m, 3H), 1,72-1,86 (m, 2H), 1,91-2,05 (m, 2H), 2,11-2,20 (m, 1H), 2,74 (m, 1H), 3,58 (s, 3H), 3,82 (q, 1H), 7,62 (m, 2H), 7,73 (m, 2H).

cis-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclohexancarboxilato de metilo

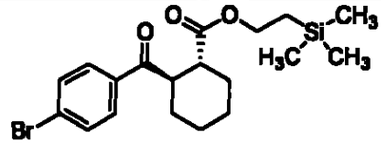
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Paso 2. Se agregaron *cis*-2-(4-bromobenzoil)ciclohexancarboxilato de metilo (1,76 g, 5,41 mmol) y ácido 4-aminofenil borónico (1,13 g, 6,49 mmol) a un matraz anhidro limpio bajo argón. Se agregaron tolueno (50 ml), EtOH (20 ml), y Na_2CO_3 3 M acuoso (14 ml, 43 mmol), y se eliminó el gas de la solución resultante durante 30 minutos usando una corriente de argón. Luego se agregó [1,1'-bis(difenilfosfina)ferroceno]dicloro paladio(II), complejo 1:1 con diclorometano (442 mg, 0,54 mmol) y se calentó la mezcla resultante a 85°C durante 16 h. Se enfrió la mezcla hasta la ta, y luego se diluyó con EtOAc y se pasó a través de un taco de Celite®. Se eliminó el solvente por evaporación rotativa. Se agregaron agua y EtOAc, y se extrajo la fase acuosa con EtOAc. Se lavaron las fases orgánicas combinadas con agua, salmuera, se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron *al vacío*. Se purificó el residuo por cromatografía flash (Biotage Flash 40M) usando 33 a 40% de acetato de etilo en hexano para producir *cis*-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]-ciclohexan-carboxilato de metilo (1,54 g, 84%). Tiempo de retención de CL-EM 3,99; *m/z* 338 (MH^+); ^{1}H RMN (400 MHz, CD_2Cl_2) δ 1,37-1,53 (m, 3H), 1,74-1,88 (m, 2H), 1,90-1,99 (m, 1H), 2,04-2,22 (m, 2H), 2,75 (m, 1H), 3,59 (s, 3H), 3,90 (q, 1H), 6,79 (m, 2H), 7,48 (m, 2H), 7,63 (m, 2H), 7,89 (m, 2H).

Intermediario H

2-(4-bromobenzoil)ciclohexancarboxilato de *trans*-(trimetilsilil)etilo

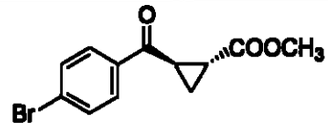


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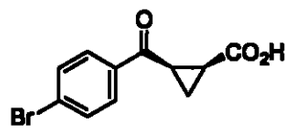
A una solución de ácido *trans*-2-(4-bromobenzoil)ciclohexancarboxílico (5,0 g, 16,07 mmol) en DCM (80 ml) se agregó 2-(trimetilsilil)etanol (2,1 g, 17,68mmol), *N,N'*-dimetilaminopiridina (98 mg, 0,80 mmol), y EDCI (4,0 g, 20,89 mmol). Se agitó la mezcla de reacción resultante a t.a. durante 2 días. Se agregó agua, y se diluyó la mezcla con DCM. Se separó la fase acuosa y se extrajo con DCM. Se lavaron las fases orgánicas combinadas con agua y salmuera, se secaron sobre sulfato de magnesio anhidro, se filtraron, y se concentraron a presión reducida. la cromatografía sobre gel de sílice (cartucho Biotage), eluyendo con EtOAc al 10% en hexano dio 2-(4-bromobenzoil)-ciclohexancarboxilato de *trans*-(trimetilsilil)etilo (2,44 g, 37%). ^{1}H RMN (400 MHz, CD_2Cl_2) δ -0,01 (s, 9H), 0,85 (m, 2H), 1,45 (m, 3H), 1,73 (m, 2H), 1,90 (m, 2H), 2,18 (m, 1H), 2,71 (m, 1H), 3,80 (m, 1H), 4,05 (m, 2H), 7,58 (d, 2H), 7,70 (d, 2H).

Intermediario I

trans-2-(4-bromobenzoil)ciclopropancarboxilato de metilo



Ácido *cis*-2-(4-Bromobenzoil)ciclopropancarboxílico

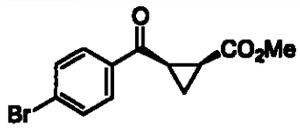


Paso 1. A una solución agitada fría (0°C) de bromobenceno (9,09 g, 57,89 mmol) y $AlCl_3$ (18,36 g, 137,84 mmol) en DCM anhidro (150 ml) se agregó 3-oxabiciclo[3,1,0]hexano-2,4-diona (5,40 g, 48,24 mmol). Se agitó la mezcla de reacción a t.a. durante 3 días. Luego se vertió la solución rojo oscuro en agua enfriada con hielo (120 ml), y se agregó HCl conc. (10 ml). Se agitó la solución durante algunos minutos, y se separaron las fases. Se extrajo la fase acuosa con DCM y se lavaron las fases orgánicas combinadas con agua, salmuera, se secaron sobre Na_2SO_4 y se concentraron para dar ácido *cis*-2-(4-bromobenzoil)ciclopropan-

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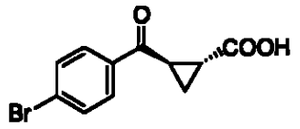
carboxílico (9,69 g, 65%). Tiempo de retención de CL-EM 2,50; *m/z* 270 (MH^+);^{1}H RMN (400 MHz, CD_2Cl_2) δ 1,54 (m, 1H), 1,85 (m, 1H), 2,37 (m, 1H), 2,88 (m, 1H), 7,65 (m, 2H), 7,90 (m, 2H).

cis-2-(4-bromobenzoil)ciclopropancarboxilato de metilo



Paso 2. A una solución de ácido *cis*-2-(4-bromobenzoil)ciclopropan-carboxílico (10,6 g, 36,63 mmol) en MeOH (250 ml) se agregó 2,2-dimetoxipropano (9,54 g, 91,59 mmol) y HCl (4,0 M en dioxano, 3,50 ml). Se agitó la solución resultante a 40°C durante 3 días, y luego se evaporó hasta la sequedad. Se purificó el residuo resultante por cromatografía flash (Biotage Flash 40M) usando 15 a 25% de acetato de etilo en hexanos para producir *cis*-2-(4-bromobenzoil)ciclopropancarboxilato de metilo (10,34 g, 99%). ^{1}H RMN (400 MHz, CD_2Cl_2) δ 1,39 (m, 1H), 1,82 (m, 1H), 2,34 (m, 1H), 2,77 (m, 1H), 3,54 (s, 3H), 7,65 (m, 2H), 7,89 (m, 2H).

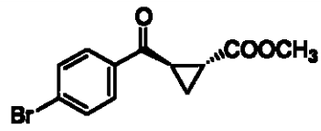
Ácido *trans*-2-(4-bromobenzoil)ciclopropancarboxílico.



Paso 3. De disolvió *cis*-2-(4-bromobenzoil)ciclopropancarboxilato de metilo (10,34 g, 36,52 mmol) en MeOH (100 ml), y luego se agregó 15 ml de solución de NaOH acuoso al 50%. Se agitó la mezcla de reacción a 40°C durante 3 días. Se eliminó el solvente por evaporación rotativa y se disolvió el residuo en agua. Se agregó HCl concentrado para ajustar la acidez hasta un pH 1. El precipitado que se formó se recogió por filtración y se secó en estufa de vacío hasta la mañana siguiente para dar ácido *trans*-2-(4-bromobenzoil)ciclopropancarboxílico (9,43 g, 95%). Tiempo de retención de CL-EM 2,51, *m/z* 270 (MH^+);^{1}H RMN (400 MHz, CD_2Cl_2) δ 1,68 (m, 2H), 2,38 (m, 1H), 3,22 (m, 1H), 7,67 (m, 2H), 7,90 (m, 2H).

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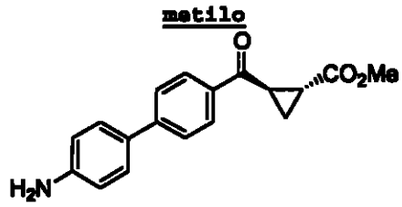
trans-2-(4-bromobenzoil)ciclopropancarboxilato de metilo.



Paso 4. A una solución de ácido *trans*-2-(4-bromobenzoil)ciclopropan-carboxílico (9,43 g, 32,59 mmol) en MeOH (200 ml) se agregó 2,2-dimetoxipropano (10,18 g, 97,77 mmol) y HCl (4,0 M en dioxano, 4,0 ml). Se agitó la solución resultante a 40°C hasta la mañana siguiente, y luego se evaporó hasta la sequedad. Se purificó el residuo resultante por cromatografía flash (Biotage Flash 40M) usando 15 a 25% de acetato de etilo en hexanos para producir *trans*-2-(4-bromobenzoil)ciclopropancarboxilato de metilo (7,7 g, 83%). ^{1}H RMN (400 MHz, CD_2Cl_2) δ 1,68 (m, 2H), 2,37 (m, 1H), 3,21 (m, 1H), 3,65 (s, 3H), 7,68 (m, 2H), 7,90 (m, 2H).

Intermediario J

Trans-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclopropancarboxilato de metilo



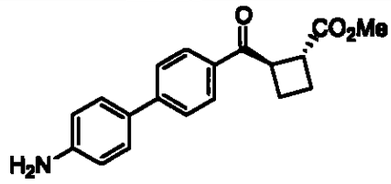
Se combinaron *trans*-2-(4-bromobenzoil)ciclopropancarboxilato de metilo (1,33 g, 4,70 mmol) y ácido 4-aminfenil borónico (0,98 g, 5,64 mmol) en un matraz seco bajo argón. Se agregaron tolueno (25 ml), EtOH (10 ml) y Na_2CO_3 3 M acuoso (7 ml, 20 mmol), y se eliminó el gas de la solución resultante durante 30 minutos usando una corriente de argón. Luego se agregó [1,1'-bis(difenilfosfin)-ferrocen]dicloro paladio(II), complejo 1:1 con diclorometano (383 mg, 0,47 mmol), y se calentó la mezcla resultante a 85°C durante 16 h. Se enfrió la mezcla hasta la ta, luego se diluyó con EtOAc y se pasó a través de un taco de Celite®. Se eliminó el solvente por evaporación rotativa. Se agregaron agua y EtOAc, y se extrajo la

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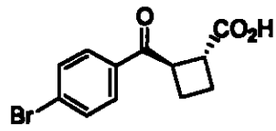
fase acuosa con EtOAc. Se lavaron las fases orgánicas combinadas con agua, salmuera, se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron *al vacío*. Se purificó el residuo por cromatografía flash (Biotage Flash 40M) usando 33 a 40% de acetato de etilo en hexano para producir *trans*-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclopropancarboxilato de metilo (0,92 g, 66%). ^{1}H RMN (400 MHz, CD_2Cl_2) δ 1,60 (m, 2H), 2,35 (m, 1H), 3,22 (m, 1H), 3,73 (s, 3H), 6,80 (m, 2H), 7,51 (m, 2H), 7,68 (m, 2H), 8,05 (m, 2H).

Intermediario K

***trans*-2-[(4'-Amino-1,1'-bifenil-4-il)carbonil]ciclobutancarboxilato de metilo**



Ácido *trans*-2-(4-bromobenzoil)ciclobutancarboxílico

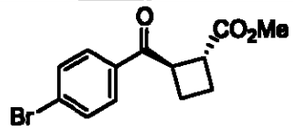


Paso 1. A una solución agitada fría (0°C) de bromobenceno (10,98 g, 69,94 mmol) y $AlCl_3$ (19,41 g, 145,71 mmol) en DCM anhidro (150 ml) se agregó anhídrido ciclobutan dicarboxílico (7,35 g, 58,28 mmol). Se agitó la mezcla de reacción a t.a. durante 3 días. Luego se vertió la solución rojo oscuro en agua enfriada con hielo (120 ml), y se agregó HCl conc. (10 ml). Se agitó la solución durante algunos minutos, se extrajo la fase acuosa con DCM, y luego se extrajeron las fases orgánicas combinadas con NaOH acuoso 1 N. Se agitó la fase de agua a t.a. hasta la mañana siguiente. Se acidificó la solución con el agregado de HCl conc. hasta un pH 1,5, se extrajo con EtOAc, y se lavaron las fases orgánicas combinadas con agua, salmuera, se secaron sobre Na_2SO_4 y se concentraron para dar ácido *trans*-2-(4-bromobenzoil)ciclobutancarboxílico (8,20 g, 49). ^{1}H RMN (400

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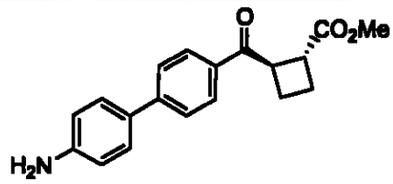
MHz, CD_2Cl_2) δ 2,20-2,44 (m, 4H), 3,67 (m, 1H), 4,21 (m, 1H), 7,64 (m, 2H), 7,80 (m, 2H).

trans-2-(4-Bromobenzoil)ciclobutancarboxilato de metilo



Paso 2. A una solución de ácido *trans*-2-(4-bromobenzoil)ciclobutan-carboxílico (8,2 g, 28,94 mmol) en MeOH (250 ml) se agregó 2,2-dimetoxipropano (3,65 g, 35,02 mmol) y HCl (4,0 M en dioxano) (2,0 ml). Se agitó la solución resultante a t.a. durante 3 días, y luego se evaporó hasta la sequedad. Se purificó el residuo resultante con cromatografía flash (Biotage Flash 40M) usando 4 a 11% de acetato de etilo en hexanos para producir *trans*-2-(4-bromobenzoil)ciclobutan-carboxilato de metilo (6,21 g, 78%). ^{1}H RMN (400 MHz, CD_2Cl_2) δ 2,14-2,39 (m, 4H), 3,62 (m, 1H), 3,68 (s, 3H), 4,24 (m, 1H), 7,63 (m, 2H), 7,80 (m, 2H).

trans-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclobutancarboxilato de metilo



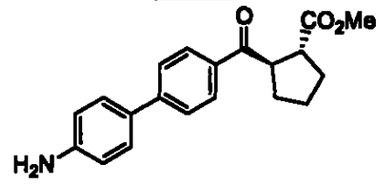
Paso 3. Se combinaron *trans*-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclobutan-carboxilato de metilo (1,25 g, 4,21 mmol) y ácido 4-aminofenil borónico (0,88 g, 5,05 mmol) en un matraz seco bajo argón. Se agregaron tolueno (25 ml), EtOH (10 ml) y Na_2CO_3 3 M acuoso (5,0 ml, 15 mmol), y se eliminó el gas de la solución resultante durante 30 minutos usando una corriente de argón. Luego se agregó [1,1'-bis(difenilfosfina)ferroceno]dicloro paladio(II), complejo 1:1 con diclorometano (343 mg, 0,42 mmol), y se calentó la mezcla resultante a 85°C durante 16 h. Se enfrió la mezcla hasta la ta, se diluyó con EtOAc, y se pasó a través de un taco de Celite®. Se eliminó el solvente por evaporación rotativa. Se agregaron agua y EtOAc, y se extrajo la fase acuosa con EtOAc. Se lavaron las fases orgánicas

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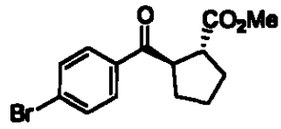
combinadas con agua, salmuera, se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron *al vacío*. Se purificó el residuo por cromatografía flash (Biotage Flash 40M) usando 29 a 37% de acetato de etilo en hexano para producir *trans*-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclobutancarboxilato de metilo (0,91 g, 70%). Tiempo de retención de CL-EM 2,24; *m/z* 310,4 (MH^+); ^{1}H RMN (400 MHz, CD_2Cl_2) δ 2,13-2,36 (m, 4H), 3,60 (m, 1H), 3,64 (s, 1H), 4,24 (m, 1H), 6,73 (m, 2H), 7,43 (m, 2H), 7,59 (m, 2H), 7,88 (m, 2H).

Intermediario L

trans-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclopentancarboxilato de metilo



trans-2-(4-Bromobenzoil)ciclopentancarboxilato de metilo

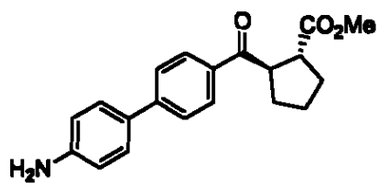


Paso 1. A una solución de ácido *trans*-2-(4-bromobenzoil)ciclopentan-carboxílico (2,0 g, 6,26 mmol) en MeOH (70 ml) se agregó 2,2-dimetoxipropano (1,63 g, 15,65 mmol) y HCl (4,0 M en dioxano) (1,0 ml). Se agitó la solución resultante a 40°C hasta la mañana siguiente y luego se evaporó hasta sequedad. Se purificó el residuo resultante por cromatografía flash (Biotage Flash 40M) usando 7 a 11% de acetato de etilo en hexanos para producir *trans*-2-(4-bromo-benzoil)ciclopentancarboxilato de metilo (1,62 g, 83%). ^{1}H RMN (400 MHz, CD_2Cl_2) δ 1,70-1,95 (m, 4H), 2,08-2,21 (m, 2H), 3,40 (m, 1H), 3,64 (s, 3H), 4,04 (m, 1H), 7,64 (m, 2H), 7,86 (m, 2H).

trans-2-[(4'-amino-1, 1'-bifenil-4-il)carbonil]ciclopentancarboxilato de metilo

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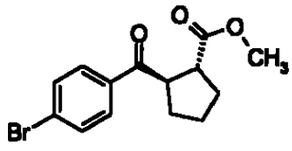
257



Paso 2. Se combinaron *trans*-2-(4-bromobenzoil)ciclopentancarboxilato de metilo (1,60 g, 5,14 mmol) y ácido 4-aminofenil borónico (1,07 g, 6,17 mmol) en un matraz seco bajo argón. Se agregaron tolueno (25 ml), EtOH (10 ml), y Na_2CO_3 3 M acuoso (8,50 ml, 25 mmol) y se eliminó el gas de la solución resultante durante 30 minutos usando una corriente de argón. Luego se agregó [1,1'-bis(difenilfosfina)-ferroceno]dicloro paladio(II), complejo 1:1 con diclorometano (419,9 mg, 0,51 mmol), y se calentó la mezcla resultante a 85°C durante 16 h. Se enfrió la mezcla hasta la ta, se diluyó con EtOAc, y se pasó a través de un taco de Celite®. Se eliminó el solvente por evaporación rotativa. Se agregaron agua y EtOAc y se extrajo la fase acuosa con EtOAc. Se lavaron las fases orgánicas combinadas con agua, salmuera, se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron *al vacío*. Se purificó el residuo por cromatografía flash (Biotage Flash 40M) usando 29 a 33% de acetato de etilo en hexano para producir *trans*-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclopentancarboxilato de metilo (1,12 g, 67%). ^1H RMN (400 MHz, CD_2Cl_2) δ 1,71-1,97 (m, 4H), 2,17 (m, 2H), 3,44 (m, 1H), 3,65 (s, 3H), 4,12 (m, 1H), 6,84 (m, 2H), 7,51 (m, 2H), 7,66 (m, 2H), 8,00 (m, 2H).

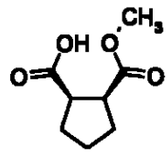
Intermediario M

Metil éster del ácido (*R,R*)-2-(4-bromo-benzoil)-ciclopentancarboxílico



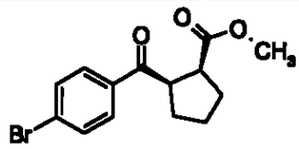
(R,R)

Monometil éster del ácido (±)-ciclopentan-1,2-dicarboxílico



Paso 1. El anhídrido tetrahidro-ciclopenta[c]furan-1,3-diona (50,0 g, 356,8 mmol, preparado como se describe en Wilkening, et al., Syn Comm. 14(3):227, 1984) se disolvió en metanol (250 ml), y luego se calentó la mezcla a 50-55°C bajo N_2 durante 5 h. El análisis de RMN no mostró restos de material de partida. Se eliminó el metanol por evaporación rotativa, y se secó el residuo *al vacío* para producir el producto deseado como un aceite incoloro (60,0 g, 98%). ^1H RMN ($CDCl_3$) δ 3,65 (s, 3H), 3,08 (m, 2H), 2,04 (m, 4H), 1,90 (m, 1H), 1,65 (m, 1H).

Metil éster del ácido (±)-*cis*-2-(4-Bromo-benzoil)-ciclopentancarboxílico



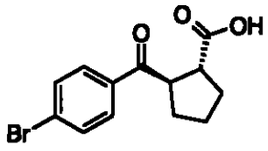
Paso 2. Una solución del monometil éster (92,0 g, 534,3 mmol), $SOCl_2$ (116,3 ml, 1,60 mol), y DMF (1 ml) en 850 ml de CH_2Cl_2 se agitó a t.a. hasta la mañana siguiente bajo N_2. El análisis de RMN mostró poco material de partida restante. Se eliminó el solvente por evaporación rotativa a <40°C, y se secó el residuo al *vacío* durante 1 h. Se disolvió este residuo seco en bromobenceno (337,6 ml, 3,2 mol), y luego se agregó en porciones $AlCl_3$ (142,5 g, 1,07 mol) a <5°C. La mezcla de reacción se tornó marrón oscuro, y se agitó a <5°C durante 4 h bajo N_2. El análisis de RMN mostró luego poco material de partida remanente. Luego se vertió la mezcla de reacción lentamente en 2 l de hielo-agua, y luego se agregó 1 l de EtOAc. Luego se agitó la mezcla durante 10 minutos, se separó la fase acuosa (superior), y se extrajo con 500 ml de EtOAc. Se lavaron las fases orgánicas combinadas con agua (2 x 1 l) y solución saturada de

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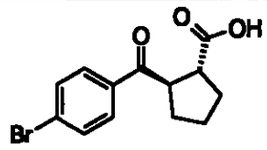
$NaHCO_3$ (200 ml), y se secaron sobre Na_2SO_4. La eliminación del solvente y el secado *al vacío* suministraron 175,0 g (>95%) del producto deseado. ^1H RMN ($CDCl_3$) δ 7,80 (d, 2H), 7,60 (d, 2H), 4,07 (m, 1H), 3,53 (s, 3H), 3,07 (m, 1H), 2,20 (m, 1H), 2,00 (m, 4H), 1,70 (m, 1H).

Ácido (±)-*trans*-2-(4-bromo-benzoil)-ciclopentancarboxílico



Paso 3. Se agregó una solución de NaOH (128,2 g, 3,2 mol) en 700 ml de agua a una solución de metil éster del ácido *cis*-2-(4-bromo-benzoil)-ciclopentancarboxílico (166,3 g, 534,3 mmol) en MeOH (700 ml). Se agitó la mezcla de reacción a t.a. hasta la mañana siguiente. El análisis de RMN mostró que quedaba poca cantidad de material de partida. Luego de eliminar aprox. 1 l del solvente por evaporación rotativa, se diluyó la mezcla con 1 l de agua. Se agregó lentamente HCl conc. con agitación a <15°C, para ajustar la acidez hasta un pH <6. Se formó un precipitado, y se continuó la agitación durante 1 h. Se filtró el precipitado sólido, y se enjuagó con agua. Se disolvió la torta del filtro seco en 1 l de EtOAc, y se secó sobre Na_2SO_4. La eliminación del solvente y el secado *al vacío* produjo el producto deseado (131 g, 83%). ^1H RMN ($CDCl_3$) δ 7,83 (d, 2H), 7,60 (d, 2H), 4,05 (m, 1H), 3,50 (m, 1H), 2,20 (m, 2H), 2,00 (m, 1H), 1,78 (m, 3H).

Ácido (*R,R*)-*trans*-2-(4-bromo-benzoil)-ciclopentancarboxílico



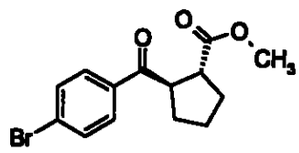
(R,R)

Paso 4. Una mezcla de ácido (±)-*trans*-2-(4-bromo-benzoil)-ciclopentan-carboxílico (114,3 g, 384,7 mmol) y (*R*)-(+)-alfa-metil-

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ZG

bencilamina (23,3 g, 192,3 mmol) en CH_3CN (1125 ml) se calentó a 90-95°C bajo N_2 para dar una solución. Se dejó enfriar la solución caliente lentamente con agitación lenta hasta la mañana siguiente. Se filtró el sólido cristalizado, y se enjuagó con CH_3CN (50 ml). El secado al vacío hasta peso constante produjo 64,5 g de sólido blanco (56% ee, por HPLC quiral). Este sólido luego se disolvió en una mezcla de solventes (258 ml de EtOH y 516 ml de agua) con calentamiento a 90-95°C bajo N_2. Se dejó enfriar la solución caliente lentamente con agitación lenta hasta la mañana siguiente. Se filtró el sólido formado, y se enjuagó con 60 ml de EtOH/Agua 1:2. Luego de secar *al vacío* hasta peso constante, este sólido blanco se agitó con HCl 1 N (500 ml) y EtOAc (500 ml) durante 10 minutos. Se separó la fase orgánica, se lavó con agua (2 x 200 ml), y se secó sobre Na_2SO_4. La eliminación del solvente y el secado *al vacío* suministraron un sólido blancuzco (30,5 g, 26,7%, >99% de ee basado en HPLC quiral). Método de HPLC quiral: columna analítica ChiralPAK AD, 5:95 iPrOH/hexanos (ambos contenían 0,1% de TFA), caudal de flujo 1,0 ml/min, los tiempos de retención fueron de 21,08 min y 23,40 min para los isómeros (*S,S*) y (*R,R*), respectivamente. Los espectros de ^1H RMN ($CDCl_3$) fueron idénticos a los obtenidos para el ácido (±)-*trans*-2-(4-bromo-benzoil)-ciclopentancarboxílico racémico.

Metil éster del ácido (*R,R*)-*trans*-2-(4-bromo-benzoil)-ciclopentancarboxílico



(R,R)

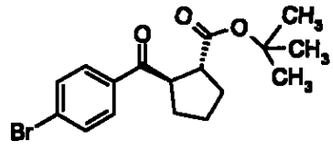
Paso 5. Una suspensión de ácido (*R,R*)-*trans*-2-(4-bromo-benzoil)-ciclopentancarboxílico (30,5 g, 102,6 mmol), MeI (9,6 ml, 154,0 mmol), y

~~261~~
261

$NaHCO_3$ (25,9 g, 307,9 mmol) en 360 ml DMF se agitó a t.a. bajo argón hasta la mañana siguiente. El análisis de RMN mostró poco material de partida restante. Se agregó agua (1 l) a la mezcla de reacción, y luego se agregó HCl concentrado lentamente con agitación a <15°C para ajustar la acidez hasta un pH <7, y se formó un precipitado. Luego se agitó la mezcla durante 1 h, se filtró el sólido y se enjuagó con agua (200 ml). Se secó el sólido *al vacío* hasta peso constante, para producir el producto deseado como un sólido amarillo claro (29,5 g, 92,5%, 94,5% de ee basado en HPLC quiral). Método de HPLC: columna analítica ChiralPAK AD, 5:95 iPrOH/hexanos (ambos contenían 0,1% de TFA), caudal de flujo 1,0 ml/min, los tiempos de retención fueron de 10,64 min y 12,98 min para los isómeros *(S,S)* y *(R,R)*, respectivamente. ^1H *RMN* ($CDCl_3$) δ 7,82 (d, 2H), 7,60 (d, 2H), 4,05 (m, 1H), 3,65 (s, 3H), 3,42 (m, 1H), 2,18 (m, 2H), 1,90 (m, 1H), 1,80 (m, 3H).

Intermediario N

Ter-butil éster del ácido (*R,R*)-2-(4-bromo-benzoil)-ciclopentancarboxílico



(R,R)

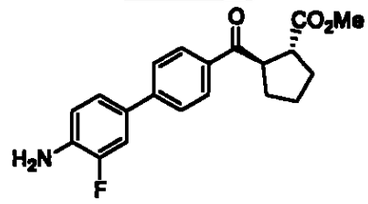
Se disolvió ácido (*R,R*)-*trans*-2-(4-Bromo-benzoil)-ciclopentancarboxílico (2,0 g, 6,73 mmol) en CH_2Cl_2 (40 ml) a ta, seguido del agregado de algunas gotas de ácido sulfúrico conc. Luego se introdujo isobutileno (aprox. 2,0 g) por suave burbujeo mientras se enfriaba la mezcla de reacción en un baño de hielo-agua. Luego se agitó la reacción a t.a. durante 60 h y se desactivó con el agregado de 40 ml de solución acuosa saturada de Na_2CO_3. Se separó la fase orgánica, se lavó con agua y se secó sobre sulfato de magnesio anhidro. La eliminación del solvente a

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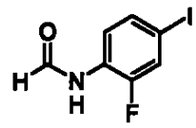
presión reducida produjo el ter-butil éster deseado como un aceite translúcido que se solidificó en reposo (1,9 g, 80% de rendimiento). ^{1}H RMN (DMSO-d_6) δ 7,90 (d, 2H), 7,88 (d, 2H), 4,00 (q, 1H), 3,10 (q, 1H), 2,10 (m, 1H), 1,90 (m, 1H). 1,50-1,80 (m, 4H), 1,30 (s, 9H).

Intermediario O

(1R,2R)-2-[(4'-Amino-3'-fluoro-1,1'-bifenil-4-il)carbonil]ciclopentancarboxilato de metilo



2-Fluoro-4-yodofenilformamida

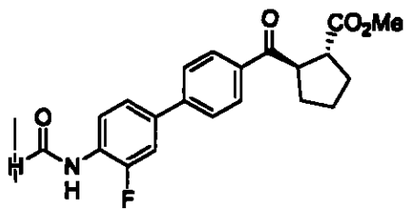


Paso 1. A una solución enfriada (0°C) de 4-yodo-2 fluoroanilina (3,05 g, 12,9 mmol) en tetrahidrofurano (15 ml) y tolueno (15 ml), se agregó lentamente una mezcla de anhídrido acético (1,39 ml, 14,7 mmol) y ácido fórmico (0,83 ml, 22,0 mmol). Se agitó la mezcla de reacción a t.a. hasta la mañana siguiente, luego se diluyó con acetato de etilo (100 ml) y HCl acuoso 1N (100 ml). Se separaron las fases, y se lavó la fase orgánica con agua y solución saturada de carbonato de sodio, y se secó sobre sulfato de sodio. Se eliminó el solvente a presión reducida para producir 2-fluoro-4-yodofenilformamida como un sólido blancuzco (3,32 g, 97%). Tiempo de ret. de CG-EM 2,27 min, *m/z* 265 (M$^+$); ^{1}H RMN (300 MHz, $CDCl_3$) δ: 7,37-7,51 (m, 3H), 8,13 (t, 1H), 8,46 (s, 1H).

(1*R*,2*R*)-2-[[3'-Fluoro-4'-(formilamino)-1,1'-bifenil-4-il]carbonil]ciclopentan-carboxilato de metilo

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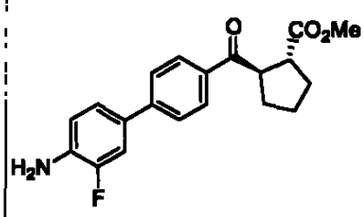
263



Paso 2. A una suspensión de 2-fluoro-4-yodofenilformamida (5,11 g, 19,28 mmol), bis(pinacolato)diboro (4,89 g, 19,28 mmol), acetato de potasio (5,67 g, 57,84 mmol), y acetato de paladio (129 mg, 0,58 mmol) en N,N-dimetilformamida (125 ml) se le burbujeó argón durante 30 minutos. Luego se calentó la mezcla de reacción a 80°C durante 3 h. Luego de enfriar la mezcla hasta la ta, se agregaron (*R,R*)-2-(4-bromobenzoil)-ciclopentancarboxilato de metilo (2,2 g, 7,35 mmol, 97% de ee), tetrakis(trifenilfosfina)paladio(0) (668 mg, 0,58 mmol), y carbonato de cesio (9,43 g, 28,92 mmol), y luego se calentó la mezcla de reacción a 80°C durante 16 h. Luego se enfrió la mezcla hasta ta, se desactivó con agua, se extrajo con acetato de etilo, y se secó sobre sulfato de magnesio anhidro. Luego se eliminó el solvente a presión reducida y se purificó el producto en bruto por cromatografía flash (Biotage 75) usando acetato de etilo/hexano 1:1 para producir 2-{[3'-fluoro-4'-(formilamino)-1,1'-bifenil-4-il]-carbonil}ciclopentan-carboxilato de metilo (4,6 g, 65%). Tiempo de retención de CL-EM 3,15 min, *m/z* 342,0 (MH^+); ^1H RMN (300 MHz, DMSO-d_6) δ 1,52-1,94 (m, 1H), 1,92-2,07 (m, 1H), 2,10-2,21 (m, 1H), 3,48 (m, 1H), 3,55 (s, 3H), 4,12 (q, 1H), 7,59 (dd, 1H), 7,62 (dd, 1H), 7,87 (d, 2H), 8,09 (d, 2H), 8,25 (t, 1H), 8,34 (s, 1H), 10,62 (s, 1H).

(1*R*,2*R*)-2-[(4'-Amino-3'-fluoro-1,1'-bifenil-4-il)carbonil]ciclopentancarboxilato de metilo

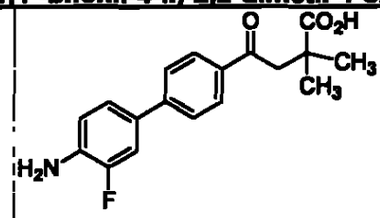
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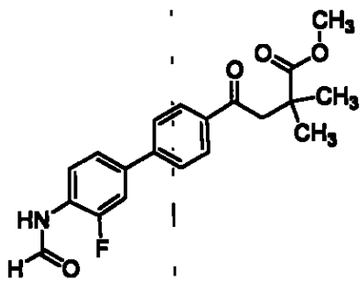
Paso 3. A una solución de 2-{[3'-fluoro-4'-(formilamino)-1,1'-bifenil-4-il]-carbonil}ciclopentancarboxilato de metilo (4,24 g, 11,48 mmol) en metanol (34 ml) se agregó HCl conc. (11,4 ml), y se agitó la solución resultante a t.a. durante 2 h. Luego se eliminó el solvente, se disolvió la mezcla residual en agua, y se ajustó la acidez de la mezcla hasta un pH ~7 mediante el lento agregado de solución acuosa saturada de bicarbonato de sodio. Luego se extrajo la mezcla con diclorometano y se lavó con solución saturada de cloruro de sodio, se secó sobre sulfato de sodio, y se eliminó el solvente *al vacío*. Luego se trituró la mezcla en bruto con acetato de etilo/hexano para producir 2-[(4'-amino-3'-fluoro-1,1'-bifenil-4-il)carbonil]ciclopentancarboxilato de metilo (3,5 g, 89%, 80% de ee). Tiempo de retención de CL-EM 3,00 min, *m/z* 370,0 (MH^+); ^{1}H RMN (300 MHz, DMSO-d_6) δ 1,52-1,84 (m, 4H), 1,97-2,02 (m, 1H), 2,14-2,18 (m, 1H), 3,24-3,33 (m, 1H), 3,56 (s, 3H), 4,08 (q, 1H), 5,47 (br s, 2H), 6,84 (t, 1H), 7,34 (dd, 1H), 7,48 (dd, 1H), 7,78 (d, 2H), 7,99 (d, 2H).

Intermediario P

4-(4'-Amino-3'-fluoro-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo



4-[3'-fluoro-4'-(formilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoato de metilo



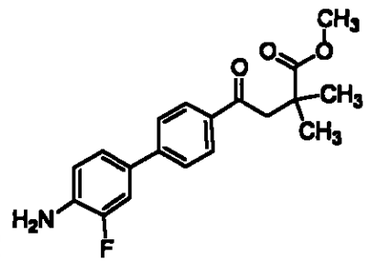
Paso 1. Una suspensión de 2-fluoro-4-yodofenilformamida (1,94 g, 7,35 mmol, preparada como se describió con anterioridad), bis(pinacolato)diboro (1,86 g, 7,35 mmol), acetato de potasio (2,16 g, 22,1 mmol), y acetato de paladio (49,4 mg, 0,22 mmol) en N,N-dimetilformamida (50 ml) se desgasificó burbujeando una corriente de argón a través de la mezcla durante 30 minutos. Luego se calentó la mezcla a 80°C durante 3 h. Luego de enfriar la mezcla hasta la ta, se agregaron 4-(4-bromofenil)-2,2-dimetil-4-oxobutanoato de metilo (2,2 g, 7,4 mmol), tetrakis(trifenilfosfina)paladio(0) (254,8 mg, 0,22 mmol) y carbonato de cesio (3,59 g, 11,0 mmol), y se calentó la mezcla de reacción a 80°C durante 16 h. Luego se enfrió la mezcla hasta ta y se agregó agua. Se extrajo la mezcla con acetato de etilo y se secaron los extractos combinados sobre sulfato de sodio. Se concentró la mezcla a presión reducida y el producto bruto se purificó por cromatografía flash (Biotage Flash 40M, acetato de etilo/hexano 1:1) para producir 4-[3'-fluoro-4'-(formilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoato de metilo (1,2 g, 46%). Tiempo de retención de CL-EM 2,80 min, *m/z* 358,1 (MH^+); ^1H RMN (300 MHz, DMSO-d_6) δ 1,19 (s, 6H), 3,36 (s, 2H), 3,51 (s, 3H), 7,56 (d, 1H), 7,69 (dd, 1H), 7,82 (d, 2H), 7,99 (d, 3H), 8,21 (t), 10,25 (s, 1H).

4-(4'-amino-3'-fluoro-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo

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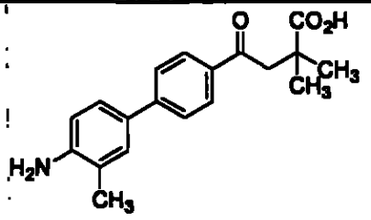
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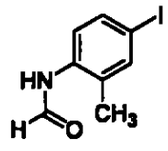
Paso 2. A una solución de metilo 4-[3'-fluoro-4'-(formilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoato (1,21 g, 3,39 mmol) en metanol (10 ml) se agregó HCl conc. (3,5 ml), y se agitó la solución resultante a t.a. durante 16 h. Luego se concentró la mezcla, se diluyó con agua, y se ajustó la acidez hasta un pH ~7 mediante el lento agregado de solución acuosa saturada de bicarbonato de sodio. Luego se extrajo la mezcla con diclorometano, y se lavaron las fases orgánicas combinadas con solución saturada de cloruro de sodio, se secaron sobre sulfato de sodio, y se concentraron a presión reducida. Luego se trituró el residuo con acetato de etilo/hexano para producir 4-(4'-amino-3'-fluoro-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo (998 mg, 89%). Tiempo de retención de CL-EM 3,11 min, *m/z* 329,9 (MH^+); ^{1}H RMN (300 MHz, $CDCl_3$) δ 1,31 (s, 6H), 3,28 (s, 2H), 3,66 (s, 3H), 6,84 (t, 1H), 7,21-7,35 (m, 2H), 7,55 (d, 2H), 7,93 (d, 2H).

Intermediario Q

4-(4'-Amino-3'-metil-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo



4-Yodo-2-metilfenilformamida

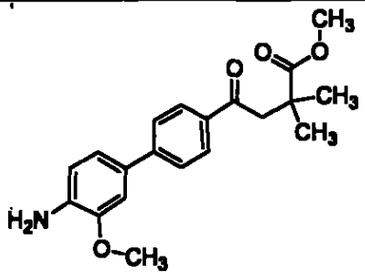


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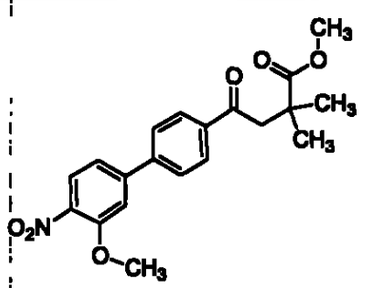
326,1 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,31 (s, 6H), 2,25 (s, 3H), 3,29 (s, 2H), 3,66 (s, 3H), 6,80 (s, 1H), 7,35 (s, 2H), 7,60 (d, 2H), 7,93 (d, 2H).

Intermediario R

4-(4'-Amino-3'-metoxi-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo



4-(3'-metoxi-4'-nitro-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo

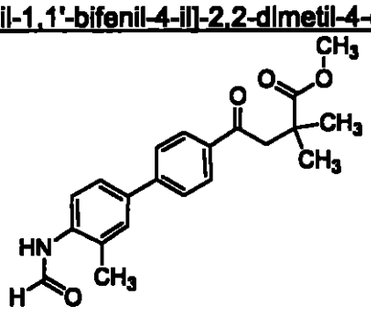


Paso 1. Una suspensión de 4-(4-bromofenil)-2,2-dimetil-4-oxobutanoato de metilo (200 mg, 0,67 mmol), bis(pinacolato)diboro (170 mg, 0,67 mmol), acetato de potasio (197 mg, 2,01 mmol), y acetato de paladio (5 mg, 0,02 mmol) en N,N-dimetilformamida (4,0 ml) se desgasificó burbujeando una corriente de argón durante 30 minutos. Luego se calentó la mezcla de reacción a 80°C durante 3 h. Luego de enfriar la mezcla hasta la ta, se agregaron 5-cloro-2-nitroanisol (125 mg, 0,67 mmol), tetrakis(trifenilfosfin)paladio(0) (23 mg, 0,02 mmol), y carbonato de cesio (327 mg, 1,0 mmol) y se calentó la mezcla de reacción a 80°C durante 16 h. Luego se enfrió la mezcla hasta ta, y se agregó agua. Se extrajo la fase acuosa con acetato de etilo y se secaron las fases orgánicas combinadas sobre sulfato de magnesio anhidro. Se eliminó el solvente a presión reducida y se purificó el residuo por cromatografía flash (Biotage Flash 40M, 1:3 acetato de etilo/hexano) para producir 4-(3'-metoxi-4'-nitro-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo (120mg, 48%). Tiempo de retención de CL-EM 3,38 min, *m/z* 371,8 (MH^+); ^1H RMN (300

268

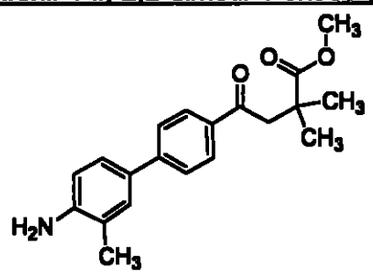
Paso 1. Este intermediario se preparó usando un procedimiento similar al que se describió con anterioridad para la 2-fluoro-4-yodofenilformamida. Tiempo de retención de CL-EM 2,43 min, *m/z* 262,0 (MH^+); ^1H RMN (300 MHz, DMSO-d_6) δ 2,14 (s, 3H), 7,49 (dd, 1H), 7,52-7,59 (m, 2H), 8,24 (s, 1H), 9,56 (s, 1H).

4-[4'-(Formilamino)-3'-metil-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoato de metilo



Paso 2. Este intermediario se preparó usando un procedimiento similar al que se describió con anterioridad para el 4-[3'-fluoro-4'-(formilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoato de metilo. Tiempo de retención de CL-EM 2,78 min, *m/z* 354,1 (MH^+); ^1H RMN (300 MHz, DMSO-d_6) δ 1,02 & 1,13 (s, 6H), 2,22 & 2,28 (s, 3H), 3,36 (s, 2H), 3,51 (s, 3H), 7,29 (d) & 7,40 (s) (2H), 7,78 (d, 2H), 7,90 & 7,96 (d, 3H), 8,46 (d) (1H), 9,82 (d) (1H).

4-(4'-Amino-3'-metil-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo

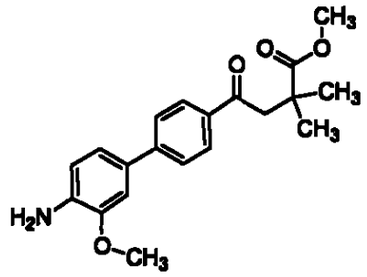


Paso 3. Este intermediario se preparó usando un procedimiento similar al que se describió con anterioridad para el 4-(4'-amino-3'-fluoro-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo. Tiempo de retención de CL-EM 2,64 min, *m/z*

269

MHz, $CDCl_3$) δ 1,19 (s, 6H), 3,36 (s, 2H), 3,51 (s, 3H), 4,02 (s, 3H), 7,21-7,24 (m, 2H), 7,64-7,69 (m, 2H), 7,93 (d, 1H), 8,00-8,04 (m, 2H).

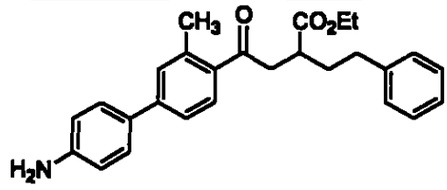
4-(4'-Amino-3'-metoxi-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo



Paso 2. A una solución de 4-(3'-metoxi-4'-nitro-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo (670 mg, 1,80 mmol) en etanol acuoso al 85% (27 ml) se agregó polvo de hierro (1,01 g, 18,04 mmol) y HCl acuoso 2 N (0,9 ml, 1,8 mmol), y la suspensión resultante se calentó a reflujo durante 2,5 h. Luego se enfrió la mezcla hasta ta, y se filtró a través de un taco de Celite®. Se agregó agua, se extrajo la mezcla con acetato de etilo, y se secaron las fases orgánicas combinadas sobre sulfato de magnesio anhidro. Se eliminó el solvente a presión reducida y se trituró el residuo con acetato de etilo/hexano para producir 4-(4'-amino-3'-metoxi-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo (410 mg, 67%). Tiempo de retención de CL-EM 2,58 min, *m/z* 342,1 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ 1,31 (s, 6H), 3,28 (s, 2H), 3,66 (s, 3H), 3,90 (s, 3H), 6,75 (d, 1H), 7,02-7,09 (m, 2H), 7,59 (d, 2H), 7,94 (d, 2H).

Intermediario S

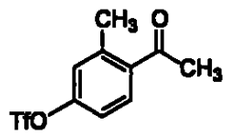
4-(4'-Amino-3-metil-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato de etilo



Trifluorometansulfonato de 4-Acetil-3-metilfenilo

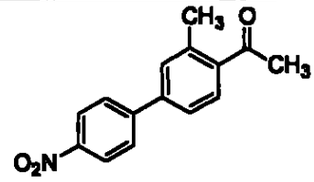
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270



Paso 1. A una solución enfriada (0-5°C) de 1-(4-hidroxi-2-metilfenil)-etanona (22,1 g, 0,147 mol) y piridina (40,0 ml, 0,500 mol) en diclorometano (100 ml) se agregó lentamente anhídrido trifluorometansulfónico (35,0 ml, 0,207 mol). Luego de completar el agregado, se retiró el baño de hielo, y se agitó la mezcla de reacción a t.a. durante 1,5 h. agua (50 ml) se agregó y se separaron las fases. Se lavó la fase orgánica con agua (2 x 20 ml) y 0,5 N acuoso HCl, se secó sobre sulfato de magnesio, y se concentró a presión reducida. Se purificó el producto en bruto por cromatografía flash (Biotage Flash 75, 10/90 acetato de etilo/hexano) para dar trifluorometansulfonato de 4-acetil-3-metilfenilo como un aceite amarillo claro (40,83 g, 90% de rendimiento). CG-EM m/z 282 (M^+), tiempo de ret. 8,20 min ^1H RMN ($CDCl_3$) δ 2,56 (s, 3H), 2,58 (s, 3H), 7,05-7,14 (m, 2H), 7,78 (d, 1H).

1-(3-Metil-4'-nitro-1,1'-bifenil-4-il)etanona

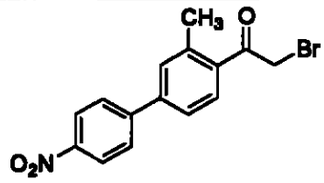


Paso 2. Una mezcla de trifluorometansulfonato de 4-acetil-3-metilfenilo (6,90 g, 24,0 mmol), ácido 4-nitrofenilborónico (3,80 g, 24 mmol), carbonato de sodio acuoso 2 N (88,0 ml), dioxano (88,0 ml), y tolueno (296 ml) se purgó con argón durante 30 minutos antes de agregar [1,1'-bis(difenilfosfina)ferroceno]dicloro paladio(II) (complejo 1:1 con diclorometano, 1,90 g, 2,30 mmol. Se calentó la mezcla de reacción a 85°C y se agitó hasta la mañana siguiente. Se separaron las fases y se lavó la fase orgánica con agua (2 x 50 ml), se secó sobre sulfato de magnesio, y se concentró a presión reducida para dar un aceite marrón. Este

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271

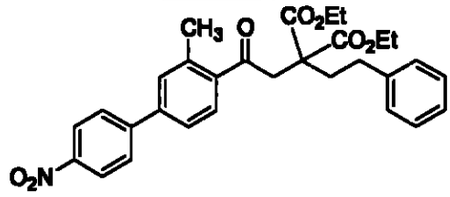
material se purificó por cromatografía flash (7 a 20% de acetato de etilo/hexano) para dar 1-(3-metil-4'-nitro-1,1'-bifenil-4-il)etanona como un sólido amarillo claro (6,12 g, 99% de rendimiento). CG-EM *m/z* 255 (M^+), tiempo de ret. 9,89 min; ^{1}H RMN ($CDCl_3$) δ 2,61 (s, 3H), 2,62 (s, 3H), 7,49-55 (m, 2H), 7,78 (d, 2H), 7,81 (d, 1H), 8,32 (d, 2H).

2-Bromo-1-(3-metil-4'-nitro-1,1'-bifenil-4-il)etanona



Paso 3. Una mezcla de 1-(3-metil-4'-nitro-1,1'-bifenil-4-il)etanona (5,66 g, 22 mmol), tribromuro de piridinio (10,63 g, 33,0 mmol), y ácido acético glacial (60 ml) se agitó a 110°C durante 3 h. Se enfrió la mezcla de reacción hasta 0-5°C, y se recolectó el producto precipitado por filtración y se lavó con pequeñas cantidades de agua, etanol, y dietil éter. El material en bruto se purificó por cromatografía flash (5:95 acetato de etilo/hexano) para dar 2-bromo-1-(3-metil-4'-nitro-1,1'-bifenil-4-il)etanona como un sólido amarillo claro (4,33 g, 59% de rendimiento). Tiempo de ret. de HPLC 3,63 min; ^{1}H RMN ($CDCl_3$) δ 2,63 (s, 3H), 2,25 (s, 2H), 7,52-7,58 (m, 2H), 7,72-7,83 (m, 3H), 8,32 (d, 2H).

2-[2-(3-Metil-4'-nitro-1,1'-bifenil-4-il)-2-oxoetil]-2-(2-feniletil)malonato de dietilo

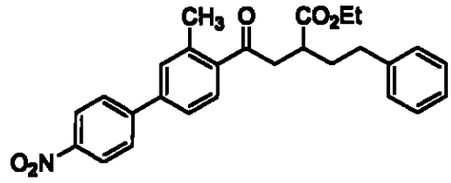


Paso 4. A una suspensión fría (0-5°C) de hidruro de sodio al 95% (3,53 g, 13,0 mmol) en tetrahidrofurano anhidro (30 ml) se agregó lentamente 2-feniletilmalonato de dietilo (3,53 g, 13 mmol). Se retiró el baño de hielo y se agitó la mezcla de reacción a t.a. durante 45 minutos. Una solución de 2-bromo-1-(3-metil-

272
272

4'-nitro-1,1'-bifenil-4-il)etanona (4,06 g, 12,0 mmol) en tetrahidrofurano anhidro (50 ml) se agregó lentamente, y se agitó la mezcla resultante a t.a. durante aproximadamente 70 h. Se agregaron acetato de etilo (80 ml) y agua (20 ml), y se separaron las fases. Se lavó la fase orgánica con agua (2 x 30 ml), se secó sobre sulfato de magnesio, y se concentró a presión reducida para dar un aceite marrón, oscuro. Este material se purificó por cromatografía flash (acetato de etilo/hexano 10:90) para dar 2-[2-(3-metil-4'-nitro-1,1'-bifenil-4-il)-2-oxoetil]-2-(2-feniletil) malonato de dietilo como un aceite amarillo claro (5,30 g, 82% de rendimiento). Tiempo de retención de CL-EM 4,01 min, *m/z* 517,9 (MH^+); ^{1}H RMN ($CDCl_3$) δ 1,23-1,35 (m, 6H), 2,41-2,50 (m, 2H), 2,56 (s, 3H), 2,59-2,66 (m, 2H), 3,71 (s, 2H), 4,21-4,32 (m, 4H), 7,13-7,19 (m, 3H), 7,22-7,30 (m, 2H), 7,49-7,55 (m, 2H), 7,73-7,82 (m, 3H), 8,31 (d, 2H).

4-(3-Metil-4'-nitro-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato de etilo.

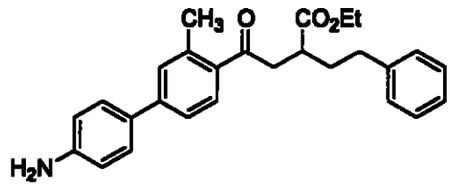


Paso 5. Una mezcla de 2-[2-(3-metil-4'-nitro-1,1'-bifenil-4-il)-2-oxoetil]-2-(2-feniletil) malonato de dietilo (4,87 g, 9,41 mmol), hidróxido de sodio acuoso 1 N (10,4 ml, 10,40 mmol), etanol (10 ml), y acetona (10 ml) se agitó a 50°C hasta la mañana siguiente. Se concentró la mezcla y se disolvió el residuo en dimetoxietano (20 ml), y se agitó a 80°C hasta la mañana siguiente. Se concentró la mezcla, y se disolvió el residuo en acetato de etilo (30 ml). Se lavó la solución con agua (2 x 5 ml), se secó sobre sulfato de magnesio, y se concentró a presión reducida. El material obtenido se purificó por cromatografía flash (acetato de etilo/hexano 10:90) para dar 4-(3-metil-4'-nitro-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato de etilo como un aceite

~~273~~
273

amarillo claro (3,53 g, 99% de rendimiento). Tiempo de retención de CL-EM 4,18 min, *m/z* 446,0 (MH^+); ^1H RMN ($CDCl_3$) δ 1,33 (t, 3H), 1,83-2,17 (m, 2H), 2,58 (s, 3H), 2,67-2,78 (m, 2H), 3,00 (dd, 1H), 3,14 (m, 1H), 3,49 (dd, 1H), 4,09 (q, 2H), 7,14-7,36 (m, 5H), 7,47-7,55 (m, 2H), 7,72-7,83 (m, 3H), 8,33 (d, 2H).

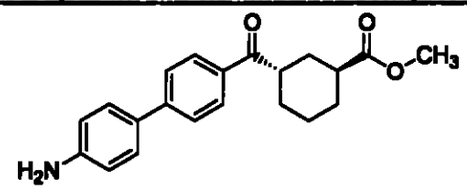
4-(4'-Amino-3-metil-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato de etilo



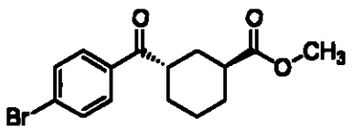
Paso 6. Una mezcla de 4-(3-metil-4'-nitro-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato de etilo (3,40 g, 7,60 mmol), polvo de hierro (4,20 g, 76,00 mmol), ácido clorhídrico acuoso 2 N (3,80 ml, 7,60 mmol), y etanol/agua 85/15 (100 ml) se agitó a reflujo durante 2,5 h. Se filtró la mezcla de reacción a través de un taco de Celite®, y se concentró para dar 4-(4'-amino-3-metil-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato de etilo como un sólido marrón claro (2,94 g, 93% de rendimiento). Tiempo de retención de CL-EM 3,23 min, *m/z* 416,1 (MH^+); ^1H RMN ($CDCl_3$) δ 1,32 (t, 3H), 1,82-2,17 (m, 2H), 2,58 (s, 3H), 2,68-2,77 (m, 2H), 2,98-3,09 (m, 2H), 3,49 (dd, 1H), 3,74 (br s, 2H), 4,10 (q, 2H), 6,79 (d, 2H), 7,12-7,37 (m, 5H), 7,38-7,54 (m, 4H), 7,78 (d, 1H).

Intermediario T

Metil éster del ácido 3-(4'-amino-bifenil-4-carbonil)-ciclohexancarboxílico

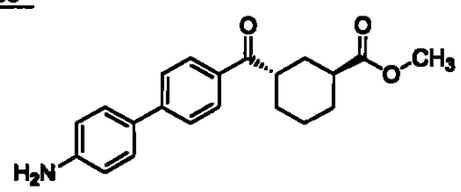


Metil éster del ácido 3-(4-bromo-benzoil)-ciclohexancarboxílico



Paso 1. A una solución de ácido *trans*-3-(4-bromobenzoil)ciclohexan-1-carboxílico (500 mg, 1,61 mmol, obtenido de Rieke Metals Inc., Lincoln, NE, EE. UU.) y 2,2-dimetoxipropano (669 mg, 6,43 mmol) en metanol (20 ml), se agregaron 5 gotas de HCl 4 M en dioxano, y esta mezcla de reacción se calentó a 50°C hasta la mañana siguiente. Se eliminó el solvente por evaporación rotativa para dar el producto metil éster del ácido 3-(4-bromo-benzoil)ciclohexan-carboxílico como un aceite marrón (500 mg, rendimiento 95,7%). ^{1}H RMN (300 MHz, DMSO) δ 7,80 (d, 2 H), 7,60 (d, 2 H), 3,70 (s, 3 H), 3,25 (m, 1 H), 2,50 (m, 1 H), 2,20-1,90 (m, 4 H), 1,70-1,50 (m, 4 H); Tiempo de retención de CL-EM 3,30 min, *m/z* 324,9 (MH^+).

Metil éster del ácido 3-(4'-amino-bifenil-4-carbonil)-ciclohexancarboxílico



Paso 2. A una solución de metil éster del ácido 3-(4-bromo-benzoil)-ciclohexancarboxílico (500 mg, 1,54 mmol) y ácido 4-aminofenil borónico (252 mg, 1,85 mmol) en tolueno (40 ml) y dioxano (10 ml), se agregó Na_2CO_3 2 N acuoso (10 ml), y se eliminó el gas de la mezcla burbujeando con una corriente de argón durante 45 minutos. Se agregó (1,1-Bis(difenilfosfin)ferrocen)-dicloropaladio (63 mg, 0,08 mmol) a la mezcla, que luego se calentó a 80°C hasta la mañana siguiente. Se enfrió la mezcla de reacción hasta ta, y luego se filtró a través de un taco de Celite®, enjuagando con acetato de etilo. Se separó la fase orgánica, se

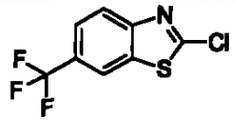
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275

lavó con agua y salmuera, y se secó (Na_2SO_4). Se eliminó el solvente por evaporación rotativa, y se purificó el residuo sólido mediante el uso de un sistema de cromatografía flash Biotage QuadUV (eluyente: hexano/EtOAc 3:1). El producto metil éster del ácido 3-(4'-amino-bifenil-4-carbonil)-ciclohexancarboxílico se obtuvo como un aceite marrón (200 mg, rendimiento 38,5%). ^{1}H RMN (300 MHz, DMSO) δ 7,90 (d, 2 H), 7,60 (d, 2 H), 7,45 (d, 2 H), 6,80 (d, 2 H), 3,70 (s, 3 H), 3,25 (m, 1 H), 2,50 (m, 1 H), 2,20 - 1,90 (m, 4 H), 1,70-1,50 (m, 4 H); Tiempo de retención de CL-EM 3,80 min (método 2), *m/z* 338,17 (MH^+).

Preparación de los Compuestos de Fórmula (VII)

Intermediario U

2-Cloro-6-(trifluorometil)-1,3-benzotiazol



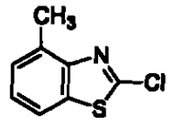
En un matraz de tres bocas provisto de un refrigerante, una suspensión de cloruro de cobre II (370 mg, 2,75 mmol) en acetonitrilo (5 ml) se trató con nitrito de *ter*-butilo (0,41 ml, 3,44 mmol) y se agitó a t.a. durante 10 minutos. Luego se agregó gota a gota una solución de 2-amino-6-trifluorometilbenzotiazol (500 mg, 2,29 mmol) en acetonitrilo (1 ml). Se calentó la mezcla a 65°C durante 30 minutos, luego se enfrió y se diluyó con un exceso de solución acuosa 1N de ácido clorhídrico. Se extrajo la mezcla con acetato de etilo. Se separó la fase orgánica, se secó ($MgSO_4$), y se concentró a presión reducida. Se obtuvo un semisólido naranja (501 mg, 92%) y se usó sin purificación adicional. ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,10-8,05 (m, 2 H), 7,74 (d, 1 H); CL-EM *m/z* 238,2 (MH^+), tiempo de ret. 3,76 min TLC R_f = 0,50 (9:1 hexanos / acetato de etilo).

Intermediario V

276.

276

2-Cloro-4-metil-1,3-benzotiazol



A una solución que contenía cloruro de cobre (II) (1,96 g, 14,61 mmol) y dimetil éster de tri(etilenglicol) (6 ml) en acetonitrilo (100 ml) se agregó nitrito de isoamilo (2,14 g, 18,27 mmol), y se agitó la mezcla de reacción a t.a. durante 30 minutos. A esta suspensión se agregó gota a gota una solución de 2-amino-4-metilbenzotiazol (2,0 g, 12,18 mmol) en dimetil éster de tri(etilenglicol) (10 ml). Se agitó la mezcla de reacción a t.a. durante 10 minutos, y luego se calentó a 50°C durante 2,5 h. Se enfrió la mezcla de reacción hasta ta, y luego se vertió con cuidado en HCl 6 M acuoso frío (400 ml). Se extrajo la solución con EtOAc. Se lavó la fase orgánica con HCl (1,0 M), agua, salmuera, se filtró y se concentró *al vacío*. Se purificó el residuo por cromatografía flash (Biotage Flash 40M) usando 5% de acetato de etilo en hexano para producir 2-cloro-4-metil-1, 3-benzotiazol (1,6 g, 71%). ^{1}H RMN (400 MHz, CD_2Cl_2) δ 2,70 (s, 3H), 7,32 (m, 2H), 7,64 (m, 1H).

Intermediario W

2-Cloro-4, 6-difluoro-1,3-benzotiazol



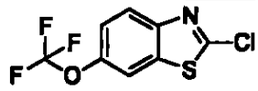
A una solución que contenía cloruro de cobre (II) (0,87 g, 6,45 mmol) y dimetil éster de tri(etilenglicol) (3 ml) en acetonitrilo (50 ml) se agregó nitrito de isoamilo (0,94 g, 8,06 mmol), y se agitó la mezcla de reacción a t.a. durante 30 minutos. A esta suspensión se agregó gota a gota una solución de 4,6-difluoro-1,3-benzotiazol-2-amina (1,0 g, 5,37 mmol) en dimetil éster de tri(etilenglicol) (5 ml). Se agitó la mezcla de reacción a t.a. durante 10 minutos, y luego se calentó a 50°C durante 2,5 h. Se enfrió la mezcla de reacción hasta ta, y luego se vertió con

~~277~~.
277

cuidado en HCl 6 M acuoso frío (200 ml). Se extrajo la solución con EtOAc. Se lavó la fase orgánica con HCl (1,0 M), agua y salmuera, se filtró y se concentró para producir 2-cloro-4,6-difluoro-1,3-benzotiazol (1,1 g, 99%). ^{1}H RMN (400 MHz, DMSO-d_6) 7,05 (m, 1H), 7,36 (m, 1H).

Intermediario X

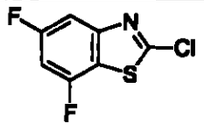
2-Cloro-6-trifluorometoxi-1,3-benzotiazol



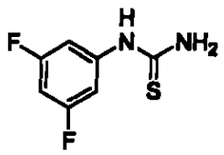
A una solución que contenía cloruro de cobre (II) anhidro (3,44 g, 25,62 mmol) y dimetil éster de tri(etilenglicol) (10 g) en acetonitrilo (150 ml) se agregó nitrito de isoamilo (4,5 ml, 32,02 mmol). Se agitó la mezcla de reacción a t.a. bajo argón durante 30 minutos. A esta suspensión se agregó gota a gota, una solución que contenía 6-trifluorometoxi-1,3-benzotiazol-2-ilamina (5 g, 21,35 mmol) y dimetil éster de tri(etilenglicol) (10 g). Se agitó la mezcla de reacción a t.a. durante 10 minutos, y luego se calentó a 50°C durante 3 h. Se enfrió la mezcla hasta la ta, se vertió con cuidado en HCl 6 N acuoso, y se extrajo con acetato de etilo. Se lavó la fase orgánica con HCl acuoso 1N y salmuera, y se concentraron a presión reducida para dar el compuesto deseado en rendimiento casi cuantitativo, que se usó sin purificación adicional en el paso siguiente.

Intermediario Y

2-Cloro-5,7-difluoro-1,3-benzotiazol



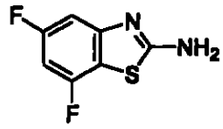
N-(3,5-Difluorofenil) tiourea



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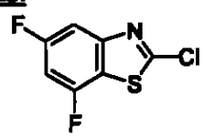
Paso 1. Se agregó cloruro de benzoílo (5,44 g, 38,73 mmol) a una solución agitada de tiocianato de amonio (3,83 g, 50,35 mmol) en acetona (80 ml) a 30°C. Se agitó la mezcla a reflujo durante 30 minutos, luego se enfrió hasta 50°C, y se agregó una solución de 3,5-difluoroanilina (5,00 g, 38,73 mmol) en acetona (10 ml) en una porción. Se agitó la mezcla a reflujo durante 30 minutos. Una solución de NaOH (5,42 g, 135,54 mmol) en agua (65 ml) se agregó, y se agitó la mezcla a reflujo durante 20 minutos y luego se enfrió hasta 20°C. Se agregó HCl concentrado para ajustar la acidez hasta un pH = 5, y luego se ajustó la mezcla hasta ser levemente alcalina con el agregado de hidróxido de amonio conc. Luego de 30 minutos, se enfrió la mezcla hasta 10°C y se extrajo con EtOAc, y se lavó la fase orgánica combinada con salmuera, se filtró, y se concentró para producir N-(3,5-difluorofenil) tiourea (3,52 g, 48%). Tiempo de ret. 1,73; *m/z* 189,0 (MH^+); ^{1}H RMN (400 MHz, MeOH-d_4) δ 6,72 (m, 1H), 7,16 (m, 2H).

5,7-Difluoro-1,3-benzotiazol-2-amina



Paso 2. A una suspensión de N-(3,5-difluorofenil) tiourea (3,40 g, 18,07 mmol) en DCE (95 ml) se agregó una solución de bromo en DCE (5 ml) por debajo de 30°C. Se calentó la mezcla a reflujo durante 2,5 h, luego se enfrió hasta 10°C, y se recolectó el precipitado formado por filtración y se lavó con DCE. Se agitó el sólido con agua (200 ml), se alcalinizó mediante tratamiento con hidróxido de amonio conc., se filtró, y se secó en estufa de vacío para producir 5,7-difluoro-1,3-benzotiazol-2-amina (3,05 g, 90%). Tiempo de ret. 2,18; *m/z* 187,1 (MH^+); ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,92 (m, 1H), 7,00 (m, 2H), 7,92 (s, 2H).

2-Cloro-5 7-difluoro-1,3-benzotiazol



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279

Paso 3. A una solución que contenía cloruro de cobre (II) (0,89 g, 6,64 mmol) y dimetil éster de tri(etilenglicol) (6 ml) en acetonitrilo (60 ml) se agregó nitrito de isoamilo (0,97 g, 8,30 mmol) y se agitó la mezcla de reacción a t.a. durante 30 minutos. A esta suspensión se agregó gota a gota una solución de 5,7-difluoro-1,3-benzotiazol-2-amina (1,03 g, 5,53 mmol) en dimetil éster de tri(etilenglicol) (20 ml) y acetonitrilo (30 ml). Se agitó la mezcla de reacción a t.a. durante 10 minutos y se calentó a 50°C durante 2,5 h. Se enfrió la mezcla de reacción hasta ta, y luego se vertió con cuidado en HCl 6 M acuoso frío (400 ml). Se extrajo la solución con EtOAc. Se lavó la fase orgánica con HCl (1,0 M), agua y salmuera, se filtró, y se concentró. Se purificó el residuo por cromatografía flash (Biotage Flash 40M) usando 5% de acetato de etilo en hexano para producir 2-cloro-5,7-difluoro-1,3-benzotiazol (0,55 g, 48%). ^{1}H RMN (400 MHz, CD_2Cl_2) 7,02 (m, 1H), 7,52 (m, 1H).

De un modo similar a los procedimientos descritos con anterioridad, se prepararon 2-cloro-1,3-benzotiazoles adicionales a partir de los correspondientes 2-amino-1,3-benzotiazoles, tales como:

(a) 2-cloro-6-etoxi-1,3-benzotiazol (CL-EM *m/z* 214,2 (MH^+), tiempo de ret. 3,09 min);

(b) 2-cloro-6-fluoro-1,3-benzotiazol (Tiempo de ret. de HPLC 2,85 min);

(c) 2-cloro-6-metil-1,3-benzotiazol (CL-EM *m/z* 184,2 (MH^+), tiempo de ret. 3,09 min);

(d) 2-cloro-5,7-dimetil-1,3-benzotiazol (CL-EM *m/z* 198,1 (MH^+), tiempo de ret. 3,36 min);

(e) 2-cloro-5,6-dimetil-1,3-benzotiazol (CL-EM *m/z* 198,2 (MH^+), tiempo de ret. 3,34 min);

(f) 2-cloro-6-metilsulfonil-1,3-benzotiazol (Tiempo de ret. de HPLC 2,18 min); and

(g) 2-cloro-5,7-difluoro-1,3-benzotiazol (TLC Rf 0,65, 40% EtOAc en hexano).

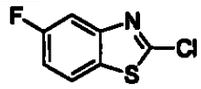
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En ciertos casos el 2-amino-1,3-benzotiazol requerido se preparó a partir de la correspondiente tiourea como se describió con anterioridad para la preparación de N-(3,5-difluorofenil) tiourea y 5,7-difluoro-1,3-benzotiazol-2-amina.

Intermediario Z

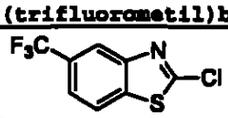
2-Cloro-5-fluoro-1,3-benzotiazol



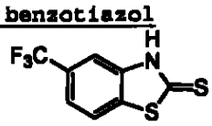
Se agregó cloruro de sulfonilo (50 µl, 0,65 mmol) puro a 5-fluoro-1,3-benzotiazol-2-tiol (100 mg, 0,54 mmol). Se agitó la mezcla a temperatura ambiente durante 1 h, luego se calentó a 60°C durante 30 minutos. Se enfrió la solución resultante hasta ta, y se vertió sobre hielo. Se recolectó el compuesto del título por filtración, se lavó con agua, y se secó al vacío. El sólido obtenido se usó sin purificación adicional; CL-EM *m/z* 188,1 (MH^+), tiempo de ret. 3,27 min.

Intermediario AA

2-Cloro-5-(trifluorometil)benzotiazol



2-Mercapto-5-(trifluorometil)benzotiazol

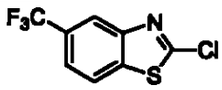


Paso 1. A una mezcla de hidruro de sodio (0,98g, 40,91 mmol) y monoetil éter de dietilenglicol (25 ml) se agregó 2-cloro-5-(trifluorometil)anilina (5,00 g, 25,57 mmol) bajo atmósfera de nitrógeno. Se agitó la mezcla resultante a t.a. durante 30 minutos, y luego se agregó disulfuro de carbono (3,89 g, 51,13 mmol). Luego se calentó la mezcla de reacción a 140°C durante 6 horas. Luego de enfriar la solución hasta ta, se precipitó el producto con el agregado de HCl conc., se recogió por filtración, y se recristalizó a partir de isopropil éter para

~~284~~
281

producir 2-mercapto-5-(trifluorometil)benzotiazol (2,65 g, 44%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,49 (s, 1H), 7,61 (d, 1H), 7,94 (d, 1H).

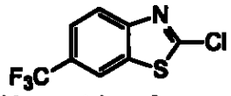
2-Cloro-5-(trifluorometil)benzotiazol



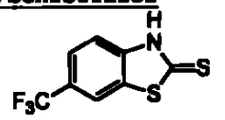
Paso 2. Se agregó cloruro de sulfonilo (9,09 g, 67,33 mmol) con agitación a 2-mercapto-5-(trifluorometil)benzotiazol (2,64 g, 11,22 mmol) durante un período de 5 minutos. Luego se dejó reposar la mezcla de reacción durante aproximadamente 1 h. Se agregó agua helada a la mezcla de reacción con agitación para descomponer el exceso de cloruro de sulfonilo, y luego se extrajo el producto con acetato de etilo. Se lavó la fase orgánica con agua (3x) y salmuera, se secó sobre Na_2SO_4 anhidro y se concentró. Se disolvió el sólido resultante en EtOAc y se filtró a través de una columna corta de gel de sílice, eluyendo con EtOAc, para dar 2-cloro-5-(trifluorometil)benzotiazol (2,50 g, 94%). CL-EM *m/z* 238,0 (MH^+), tiempo de ret. 2,55 min; ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,81 (d, 1H), 8,38 (m, 2H).

Intermediario BB

2-Cloro-6-(trifluorometil)benzotiazol



2-Mercapto-6-(trifluorometil)benzotiazol



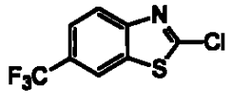
Paso 1. Una mezcla de 2-cloro-4-trifluorometilanilina (15,0 g, 76,7 mmol) y *O*-etil ditiocarbonato de potasio (29,5 g, 184,1 mmol) en 75 ml de DMF anhidro se calentó a 130°C hasta la mañana siguiente bajo atmósfera de nitrógeno. Se enfrió la mezcla de reacción hasta ta, y luego se agregó solución 1 N de HCl (200 ml) con agitación para inducir

282.

282

la precipitación. Luego se agitó la mezcla durante 30 minutos, se recolectó el precipitado sólido por filtración y se enjuagó con agua. Se disolvió la torta del filtro en 100 ml de EtOAc, y se secó la solución sobre Na_2SO_4. Se eliminó el EtOAc por evaporación rotativa, y se secó el residuo *al vacío* para producir el producto deseado como un sólido blanco (18,0 g, 99%). ^1H RMN (DMSO-d_6) δ 14,00 (bs, 1 H), 8,20 (s, 1 H), 7,70 (d, 1 H), 7,40 (d, 1 H); GC- EIMS *m/z* 235 (M^+).

2-Cloro-6-(trifluorometil)benzotiazol



Paso 2. Se agregó cloruro de sulfonilo (40 ml) con agitación a 2-mercapto-6-(trifluorometil)benzotiazol (18,0 g, 76,7 mmol) a <20°C bajo atmósfera de nitrógeno, y luego se agitó la suspensión a t.a. durante 2 h. La mezcla de reacción se vertió en agua helada con agitación. Se formó precipitación, y se continuó la agitación durante 2 h. Se filtró el precipitado sólido, y se enjuagó con agua. La torta del filtro húmeda se disolvió en 100 ml de EtOAc, y se lavó la solución con 100 ml de agua y 50 ml de solución acuosa saturada de $NaHCO_3$, luego se secó sobre Na_2SO_4. Se eliminó el EtOAc por evaporación rotativa, y se secó el residuo *al vacío* para producir el producto deseado como un sólido amarillo claro (16,5 g, 91%). GC-EIMS *m/z* 237 (M^+); ^1H RMN ($CDCl_3$) δ 8,10 (s, 1 H), 8,00 (d, 1 H), 7,70 (d, 1 H).

De un modo similar a los procedimientos descritos con anterioridad, se prepararon 2-cloro-1,3-benzotiazoles adicionales a partir de los correspondientes 2-mercapto-1,3-benzotiazoles, tales como 2-cloro-5-fluoro-1,3-benzotiazol (CL-EM *m/z* 188,1 (MH^+), tiempo de ret. 3,27 min). Los 2-cloro-1,3-benzotiazoles adicionales se obtuvieron en el mercado, tales como 2-cloro-benzotiazol, 2,6-diclorobenzotiazol, 2,4-

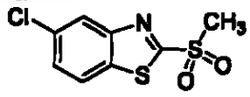
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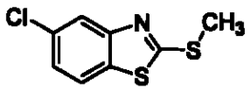
diclorobenzotiazol, 2-cloro-6-metoxi-1,3-benzotiazol, 2-cloro-5-metoxi-1,3-benzotiazol, y 2-cloro-6-nitro-1,3-benzotiazol. Ciertos 2-bromo-tiazoles se obtuvieron en el mercado, tales como 2-bromo-tiazol y 2-bromo-5-nitro-tiazol.

Intermediario CC

5-Cloro-2-metansulfonilbenzotiazol

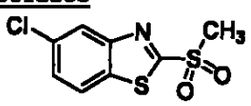


5-Cloro-2-metilsulfanil-benzotiazol



Paso 1. A 5-clorobenzotiazol-2-tiol (1,00 g, 4,96 mmol) en tetrahidrofurano anhidro (20 ml) se agregó carbonato de potasio en polvo (1,37 g, 9,92 mmol) como un sólido. Luego se agregó yodometano (0,62 ml, 1,41 g, 9,92 mmol) puro a la mezcla, con rápida agitación. Luego de agitar durante 18 h, se eliminaron los sólidos por filtración. Se concentró el filtrado al vacío para suministrar el compuesto del título como un sólido amarillo con aspecto de cera (1,0 g, 93%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,77 (s, 1 H), 7,57 (d, 1 H), 7,21-7,17 (m, 1 H), 2,72 (s, 3 H); CL-EM *m/z* 216,2 (MH^+), tiempo de retención 3,20 minutos. TLC R_f 0,72 (2:1 hexanos / acetato de etilo).

5-Cloro-2-metansulfonilbenzotiazol



Paso 2. A una solución a 0°C de 5-cloro-2-metilsulfanil-benzotiazol (1,00 g, 4,64 mmol) en diclorometano (25 ml) se agregó ácido 3-cloroperoxibenzoico (50%, 3,20 g, 9,27 mmol). Se agitó la solución a t.a. durante 24 h, y se agregó solución acuosa saturada de $Na_2S_2O_5$ para destruir cualquier peracido sin reaccionar. Se separaron las fases, y se lavó la fase orgánica con solución

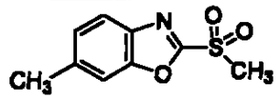
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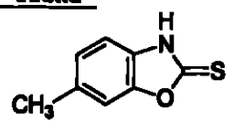
acuosa saturada de bicarbonato de sodio y salmuera, luego se secó ($MgSO_4$) y se concentró a presión reducida a un sólido amarillo. Se trituró el sólido en bruto con hexanos, se recolectó por filtración, y se secó al aire para dar el compuesto del título como un sólido amarillo pálido (0,96 g, 83%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,17 (s, 1 H), 8,04 (d, 1 H), 7,41 (dd, 1 H), 3,40 (s, 3 H); CL-EM *m/z* 248,0 (MH^+), tiempo de retención 3,05 minutos. TLC R_f 0,36 (hexanos/acetato de etilo 2:1).

Intermediario DD

6-Metil-2-(metilsulfonil)-1,3-benzoxazol

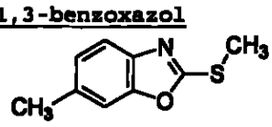


6-Metil-1,3-benzoxazol-2(3H)-tiona



Paso 1. Una mezcla de 6-amino-m-cresol (593,7 mg, 4,82 mmol) y xantato de O-etilo y potasio (850 mg, 5,30 mmol) en piridina (10 ml) se agitó y se calentó a reflujo durante 2 h. Se enfrió hasta ta, se vertió dentro de una mezcla de hielo-agua (40 ml), y HCl concentrado (4 ml). Se recolectó el sólido, se lavó con agua, y se secó en la capucha hasta la mañana siguiente y luego en estufa de vacío a 45°C durante 3 h. El producto 6-metil-1,3-benzoxazol-2(3H)-tiona se obtuvo como un polvo beige (735 mg, rendimiento 92,3%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 7,10 (s, 1 H), 7,03 (d, 2 H), 2,42 (s, 3H); Tiempo de retención de CL-EM 2,37 min (método 2), *m/z* 166,0 (MH^+).

6-Metil-2-(metilsulfanil)-1,3-benzoxazol

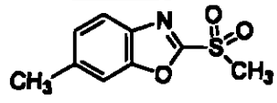


Paso 2. Se disolvió 6-metil-1,3-benzoxazol-2(3H)-tiona (375 mg, 2,27 mmol) en THF (2,0 ml), y se agregaron yodometano (1610,8 mg, 11,35 mmol) y carbonato de potasio (627,36 mg, 4,54 mmol). Esta mezcla de reacción se agitó vigorosamente a t.a. hasta la mañana siguiente. Se

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285

filtró la mezcla de reacción y se enjuagó el sólido con THF adicional. Se concentró el filtrado *al vacío* a un sólido amarillo. Se repartió el sólido entre acetato de etilo y agua. Se separó la fase orgánica y se lavó con salmuera, se secó con $MgSO_4$, y se concentró. Se secó el sólido durante 1 h en estufa a 50°C. El producto 6-metil-2-(metilsulfanil)-1,3-benzoxazol se obtuvo como un sólido amarillo (145 mg, 35,6%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 7,50 (d, 1 H), 7,20 (s, 1 H), 7,10 (d, 1 H), 2,78 (s, 3 H), 2,42 (s, 3 H); Tiempo de retención de CL-EM 2,90 min (método 2), *m/z* 180,1 (MH^+).

6-Metil-2-(metilsulfonil)-1,3-benzoxazol



Paso 3. Se agregó ácido *meta*-cloroperoxibenzoico (1,37 g, 6,14 mmol) a una solución de 6-metil-2-(metilsulfanil)-1,3-benzoxazol (500 mg, 2,79 mmol) en diclorometano (20 ml) a 0°C. Se entibió la reacción hasta ta y se agitó a t.a. durante a total de 48 h. Se transfirió la reacción a un embudo de decantación, se lavó con $NaHCO_3$ acuoso saturado (3 x 5 ml) y salmuera (10 ml), se secó con $MgSO_4$, y se concentró sin calentar. El producto 6-metil-2-(metilsulfonil)-1,3-benzoxazol (200 mg, 33,9%) se obtuvo como un sólido amarillo pálido. Tiempo de ret. de CG-EM 10,53 min, *m/z* 211 (MH^+).

De un modo similar al del ejemplo precedente, se prepararon los siguientes 2-(metilsulfonil)-1,3-benzoxazoles:

(a) 6-cloro-2-(metilsulfonil)-1,3-benzoxazol;

(b) 6-metoxi-2-(metilsulfonil)-1,3-benzoxazol;

(c) 5-metil-2-(metilsulfonil)-1,3-benzoxazol;

(d) 4-metil-2-(metilsulfonil)-1,3-benzoxazol;

(e) 2-(metilsulfonil)-5,6,7,8-tetrahidronafto[2,3-d][1,3]oxazol;

(f) 5-fluoro-2-(metilsulfonil)-1,3-benzoxazol;

(g) 6-fluoro-2-(metilsulfonil)-1,3-benzoxazol;

(h) 5-isopropil-2-(metilsulfonil)-1,3-benzoxazol;

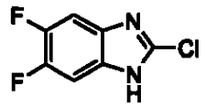
(i) 5-*n*-propil-2-(metilsulfonil)-1,3-benzoxazol; y

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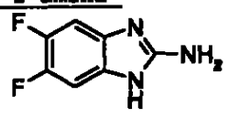
(j) 5,6-dimetil-2-(metilsulfonil)-1,3-benzoxazol.

Intermediario EE

2-Cloro-5,6-difluoro-1H-benzoimidazol

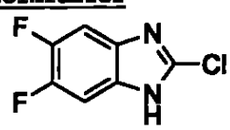


5,6-Difluoro-1H-bencimidazol-2-amina



Paso 1. El procedimiento usado fue similar al mencionado en J. Med. Chem. 40: 811-818, 1997. Una solución de 1,2-diamino-4,5-difluorobenceno (500 mg, 3,47 mmol) en agua (5 ml) se enfrió hasta 0°C y luego se trató con una solución de bromuro de cianógeno (0,83 ml, 4,16 mmol, 5 M en acetonitrilo) y bicarbonato de sodio sólido (583 mg, 6,94 mmol). Se agitó la solución a t.a. hasta la mañana siguiente y luego se concentró *al vacío*. Se suspendió el residuo oscuro en etanol y se calentó a reflujo durante 15 minutos. Se filtró la suspensión caliente, enjuagando con etanol caliente, y se concentró el filtrado *al vacío* para producir 5,6-difluoro-1H-bencimidazol-2-amina (580 mg, 59%), que se usó en el paso siguiente sin purificación adicional. CL-EM *m/z* 170,2 (MH^+), tiempo de ret. 0,85 min; ^1H RMN (300 MHz, DMSO-d_6) δ 6,30 (br s, 2H), 7,06 (dd, 2H), 10,79 (br s, 1H).

2-Cloro-5,6-difluoro-1H-benzoimidazol



Paso 2. El procedimiento usado fue similar al mencionado en J. Med. Chem. 40: 811-818, 1997. A una mezcla de cloruro de cobre (II) (795 mg, 5,91 mmol) en acetona (20 ml) se agregó nitrito de ter-butilo (0,53 ml, 4,43 mmol). Se agitó la mezcla de reacción a t.a. durante 20 minutos, luego se agregó 5,6-difluoro-1H-benzoimidazol-2-amina (500 mg, 2,96 mmol), y se calentó la

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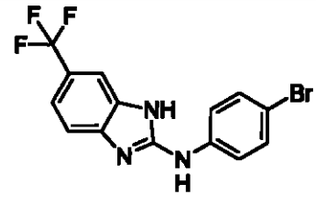
mezcla a reflujo durante 2 h (con porciones adicionales de nitrito de ter-butilo agregado cada 0,5 h). La mezcla de reacción luego se enfrió hasta ta, se trató con HCl 2 N, y se extrajo con acetato de etilo. La fase orgánica se secó sobre sulfato de sodio y se concentró *al vacío* para producir 2-cloro-5,6-difluoro-1H-benzoimidazol (580 mg, 73%), que se usó sin purificación adicional en el paso siguiente. CL-EM *m/z* 189,2 (MH^+), tiempo de ret. 1,96 min; ^1H RMN (300 MHz, DMSO-d_6) δ 7,62 (t, 2H), 13,5 (br s, 1H).

Ciertos 2-clorobenzoimidazoles se obtuvieron en el mercado tales como 2-clorobenzoimidazol y 2-cloro-5-metoxibenzoimidazol.

Preparación de los Compuestos de Fórmula (IX)

Intermediario FF

N-(4-Bromofenil)-6-(trifluorometil)-1H-bencimidazol-2-amina



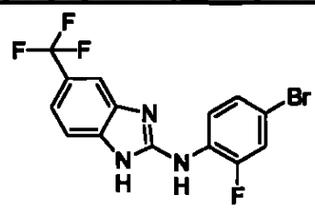
Se diluyó 1,2-diamino-5-trifluorometilbenceno (0,25 g, 1,42 mmol) en tolueno (5 ml) y se trató con 4-bromofenilisotiocianato (0,30 g, 1,42 mmol). La solución oscura se agitó a 100°C durante 15 minutos, luego se trató con 1,3-diciclohexilcarbodiimida (0,44 g, 2,13 mmol). Se mantuvo la reacción a 100°C durante 5 h. Se concentró la reacción y se repartió entre acetato de etilo y agua. Se separó la fase orgánica, se secó ($MgSO_4$), y se concentró a presión reducida. El aceite marrón oscuro se purificó por cromatografía flash sobre gel de sílice, eluyendo con un gradiente de hexanos/acetato de etilo 9:1 hasta 100% de acetato de etilo. El compuesto del título se obtuvo como un sólido rosa claro (0,50 g, 30%). ^1H RMN (300 MHz, DMSO-d_6) δ 11,3 (d amplio, 1 H), 9,87 (d, 1 H), 7,50 (d, 2 H), 7,61 (d, 1 H), 7,55-7,42 (m, 3 H), 7,35-7,30 (m, 1 H); CL/EM *m/z* 356,2 (MH^+), tiempo de retención 2,33 minutos.

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288

Intermediario GG

N-(4-Bromo-2-fluorofenil)-N-[5-(trifluorometil)-1H-benzoimidazol-2-il]amina

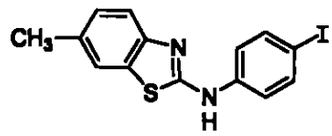


Se diluyó 1,2-diamino-5-trifluorometilbenceno (0,50 g, 2,84 mmol) en diclorometano (5 ml) y se trató con 4-bromo-2-fluoro-fenilisotiocianato (0,66 g, 2,84 mmol). La solución oscura se agitó a 45°C durante 15 minutos, luego se agregó 1,3-diciclohexilcarbodiimida (0,44 g, 2,13 mmol) de una vez. Se calentó la reacción en un baño de aceite a 45°C hasta la mañana siguiente, luego se enfrió y se concentró a presión reducida. El residuo oscuro se diluyó con acetato de etilo, y se lavó la fase orgánica con agua. Se secó la fase orgánica ($MgSO_4$) y se concentró *al vacío*. El aceite marrón oscuro resultante se purificó por cromatografía flash sobre gel de sílice eluido sobre un gradiente de 9:1 hexanos / acetato de etilo a 100% de acetato de etilo. Se recogió el compuesto del título como un sólido rosa claro (0,60 g, 57%). ^1H RMN (300 MHz, DMSO-d_6) δ 11,3 (d amplio, 1H), 9,87 (d, 1H), 7,50 (d, 2H), 7,61 (d, 1H), 7,55-7,41 (m, 3H), 7,35-7,30 (m, 1H); CL/EM *m/z* 356,2 (MH^+), tiempo de retención 2,33 minutos.

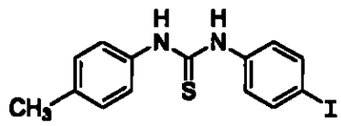
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Intermediario HH

N-(4-Yodofenil)-6-metil-1,3-benzotiazol-2-amina

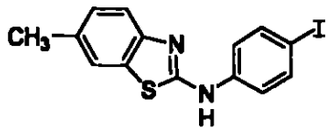


N-(4-Yodofenil)-N'-(4-metilfenil) tiourea



Paso 1. Una solución de tiocianato de *p*-tolilo (0,65 g, 4,35 mmol) y *p*-yodoanilina (1,00 g, 4,57 mmol) en EtOH se calentó a reflujo durante 3 h. Luego se diluyó la mezcla de reacción con EtOH y se recolectó el precipitado por filtración, se lavó con EtOH y éter, y se secó en estufa de vacío para dar N-(4-yodofenil)-N'-(4-metilfenil) tiourea (1,32 g, 90% de pureza, 74% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,78 (s, 3H), 7,12 (d, 2H), 7,29 (m, 4H), 7,63 (m, 2H), 9,72 (s, 1H), 9,76 (s, 1H).

N-(4-Yodofenil)-6-metil-1,3-benzotiazol-2-amina



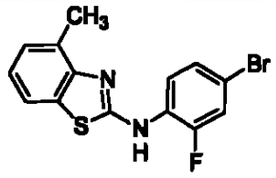
Paso 2. Se trató una suspensión de N-(4-yodofenil)-N'-(4-metilfenil) tiourea (0,62 g, 4,68 mmol) en cloroformo (23 ml) con una solución de bromo (2,65 g, 16,59 mmol) en cloroformo (1 ml). Se agitó la mezcla de reacción a t.a. durante 5 minutos y luego se calentó a 50°C durante 5 minutos. Luego se dejó enfriar la mezcla de reacción, y se trató con ácido sulfuroso hasta que desapareció el color naranja. La mezcla de reacción se neutralizó por tratamiento con hidróxido de amonio conc.. Luego se agregó más cloroformo para disolver el precipitado. Se separaron las fases, y se lavó la fase orgánica con agua y salmuera, se secó sobre sulfato de sodio, se filtró y se concentró para dar N-(4-yodofenil)-6-metil-1,3-benzotiazol-2-

290

amina (0,6 g, 97%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,36 (s, 3H), 7,12 (m, 1H), 7,48 (d, 1H), 7,60 (m, 3H), 7,65 (m, 2H), 10,50 (s, 1H).

Intermediario II

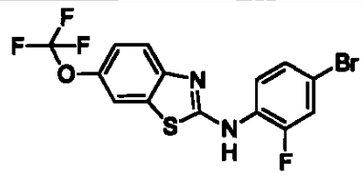
***N*-(4-Bromo-2-fluorofenil)-4-metil-1,3-benzotiazol-2-amina**



A una solución de 2-cloro-4-metil-1,3-benzotiazol (0,25 g, 1,36 mmol) en n-BuOH (8 ml) se agregó 4-bromo-2-fluoroanilina (0,52 g, 2,72 mmol) y HCl (4,0 M en dioxano, 0,5 ml). Se calentó la reacción a 90°C hasta la mañana siguiente. Se eliminó el solvente por evaporación rotativa y se agregó HCl 1 N acuoso. Se separó la fase acuosa y se extrajo con EtOAc. Se lavaron las fases orgánicas combinadas con HCl acuoso 1 N y salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró *al vacío*. El residuo se absorbió en MeOH y se recolectó el precipitado por filtración, se lavó con MeOH, y se secó en estufa de vacío para dar N-(4-bromo-2-fluorofenil)-4-metil-1,3-benzotiazol-2-amina (0,41 g, 89%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,62 (s, 3H), 7,07 (t, 1H), 7,15 (d, 1H), 7,36 (m, 2H), 7,51 (d, 1H), 8,72 (t, 1H).

Intermediario JJ

***N*-(4-Bromo-2-fluorofenil)-*N*-(6-trifluorometoxi-1,3-benzotiazol-2-il)amina**



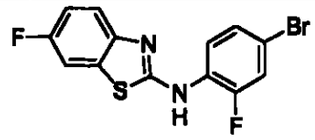
En un balón de 250 ml, se combinaron 2-cloro-6-trifluorometoxi-1,3-benzotiazol (5,36 g, 21,14 mmol) y 4-bromo-2-fluoroanilina (4,82 g, 25,36 mmol) en 100 ml de n-butanol que contenía 1% de HCl 4,0 M en dioxano, y se calentó a 90°C hasta la mañana siguiente. Se enfrió la mezcla hasta la ta y se eliminó el solvente a

291

presión reducida. Se agregó acetato de etilo (50 ml), y se sometió la mezcla a ultrasonido suspendiendo el balón en un baño de ultrasonido durante 30 minutos. Se filtró la mezcla, y se concentró el filtrado a presión reducida. Se agregó acetonitrilo (50 ml) a la mezcla, que luego se sometió a ultrasonido durante 30 minutos y luego se filtró para suministrar el producto como un sólido blanco (5 g, 58%). CL-EM *m/z* 409,1 (MH^+), tiempo de ret. 4,02 min.

Intermediario KK

***N*-(4-Bromo-2-fluorofenil)-*N*-(6-fluoro-1,3-benzotiazol-2-il)amina**



De un modo similar al que se describió con anterioridad para la preparación de *N*-(4-bromo-2-fluorofenil)-4-metil-1,3-benzotiazol-2-amina y *N*-(4-bromo-2-fluorofenil)-*N*-(6-trifluorometoxi-1,3-benzotiazol-2-il)amina, usando 2-cloro-6-fluoro-1,3-benzotiazol y 2-fluoro-4-bromoanilina, se preparó el producto deseado como un sólido blanco (78% de rendimiento). ^{1}H RMN (400 MHz, 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).

De un modo similar a los procedimientos descritos con anterioridad, se prepararon las siguientes *N*-(4-bromofenil)-*N*-(1,3-benzotiazol-2-il)aminas a partir de 4-bromoanilinas y 2-cloro-1,3-benzotiazoles apropiados:

(a) *N*-(4-bromofenil)-*N*-(5-trifluorometil-1,3-benzotiazol-2-il)amina
(CL-EM *m/z* 373,0 (MH^+), tiempo de ret. 3,92 min);

(b) *N*-(4-bromo-2-fluorofenil)-*N*-(5-trifluorometil-1,3-benzotiazol-2-il)amina
(CL-EM *m/z* 391,0 (MH^+), tiempo de ret. 4,04 min (método 2));

(c) *N*-(4-bromo-2-fluorofenil)-*N*-(6-trifluorometil-1,3-benzotiazol-2-il)amina
(CL-EM *m/z* 391,0 (MH^+), tiempo de ret. 3,95 min);

(d) *N*-(4-bromo-2-fluorofenil)-*N*-(5,7-dimetil-1,3-benzotiazol-2-il)amina
(CL-EM *m/z* 353,1 (MH^+), tiempo de ret. 4,09 min);

292

(e) *N*-(4-bromo-2-fluorofenil)-*N*-(5,7-difluoro-1,3-benzotiazol-2-il)amina (CL-EM *m/z* 359,1 (MH^+), tiempo de ret. 3,86 min);

(f) *N*-(4-bromo-2-fluorofenil)-*N*-(6-metoxi-1,3-benzotiazol-2-il)amina (CL-EM *m/z* 353,2 (MH^+), tiempo de ret. 3,55 min);

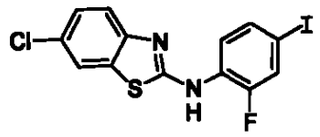
(g) *N*-(4-bromo-2-fluorofenil)-*N*-(1,3-benzotiazol-2-il)amina (CL-EM *m/z* 323,1 (MH^+), tiempo de ret. 3,55 min);

(h) *N*-(4-bromofenil)-*N*-(6-isopropil-1,3-benzotiazol-2-il)amina (CL-EM *m/z* 347,2 (MH^+), tiempo de ret. 4,44 min); y

(i) *N*-(4-bromo-2-fluorofenil)-*N*-(6-isopropil-1,3-benzotiazol-2-il)amina (CL-EM *m/z* 365,2 (MH^+), tiempo de ret. 4,57 min).

Intermediario LL

N-(4-Yodo-2-fluorofenil)-6-cloro-1,3-benzotiazol-2-amina

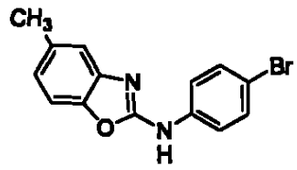


Una mezcla de 2,6-diclorobenzotiazol (1,0 g, 4,9 mmol) y 2-fluoro-4-yodoanilina (2,32 g, 9,8 mmol) en 20 ml BuOH se agitó a 90°C, y luego se agregó HCl (4 M en dioxano, 1,0 ml). Se agitó la mezcla de reacción con calor a 90°C hasta la mañana siguiente, bajo argón. El análisis de RMN luego mostró poca cantidad de 2,6-diclorobenzotiazol restante. Luego se eliminó el BuOH por evaporación rotativa, se agregaron EtOAc (100 ml) y HCl acuoso 1 N (100 ml). Se separó la fase orgánica y se lavó con HCl acuoso 1 N (100 ml), solución saturada de $Na_2O_2S_3$ (50 ml), agua (100 ml), y luego se secó sobre Na_2SO_4. La eliminación del solvente a presión reducida produjo un residuo, que se trituró con EtOAc (10 ml) y hexanos (40 ml). Se filtró el sólido y se secó *al vacío* hasta un peso constante, para producir el producto deseado como un sólido púrpura claro (0,75 g, 38%). ^1H RMN (DMSO-d_6) δ 10,45 (s, 1H), 8,35 (t, 1H), 7,95 (s, 1H), 7,70 (d, 1H), 7,58 (d, 2H), 7,30 (d, 1H).

Intermediario MM

N-(4-Bromofenil)-N-(5-metil-1,3-benzoxazol-2-il)amina

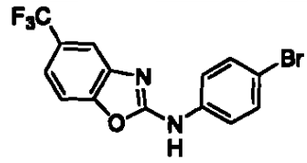
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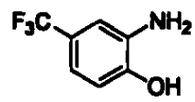
En un balón de 250 ml, se agitaron 1-bromo-4-isotiocianatobenceno (4,28 g, 20 mmol) y 2-amino-4-metil-fenol (2,46 g, 20 mmol) en 120 ml etanol a t.a. hasta la mañana siguiente. La formación de *N*-(4-bromofenil)-*N'*-(2-hidroxi-5-metilfenil)tiourea se confirmó por CL-EM. A la mezcla, 1,5 eq. se agregó clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDCI), y se agitó la reacción a t.a. durante otras 2 h. Luego se calentó la mezcla de reacción a reflujo durante 6 h. Se enfrió la mezcla hasta la ta y se eliminó el solvente a presión reducida. Se disolvió el sólido en EtOAc y se lavó con HCl acuoso 2 N y H_2O. Se secó la fase orgánica ($MgSO_4$) y se eliminó el solvente a presión reducida. El sólido obtenido se sometió a ultrasonido en 30 ml de éter y se filtró para dar el compuesto deseado (3,64 g, 60%). ^1H RMN (400 MHz, DMSO-d_6) δ 10,70 (s, 1 H), 7,70 (m, 2 H), 7,55 (m, 2 H), 7,35 (d, 1 H), 7,25 (s, 1 H), 6,95 (d, 1 H), 2,40 (s, 3 H). CL-EM *m/z* 303,3 (MH^+), tiempo de ret. 3,46 min.

Intermediario NN

N-(4-Bromofenil)-5-(trifluorometil)-1,3-benzoxazol-2-amina



2-Amino-4-(trifluorometil)fenol

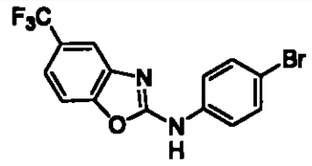


Paso 1. A una suspensión de hidróxido de paladio (3,05 g, 21,7 mmol) en metanol se agregó a solución en metanol de 2-nitro-4-(trifluorometil)fenol (1,00 g,

294

4,8 mmol) seguido de formiato de amonio sólido (3,04 g, 48,3 mmol). Se calentó la mezcla a 85°C y se monitoreó por TLC. Se dejó enfriar la reacción completada hasta ta y se filtró a través de un taco de Celite®, lavando con acetato de etilo. Se concentró el filtrado a presión reducida para dar el compuesto del título (0,58 g, 67%). CL-EM *m/z* 178,1 (MH^+), tiempo de retención 0,55 minutos.

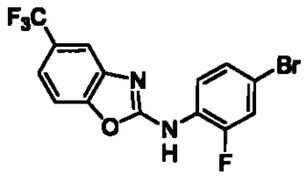
N-(4-Bromofenil)-5-(trifluorometil)-1,3-benzoxazol-2-amina



Paso 2. Se agitaron 2-amino-4-(trifluorometil)fenol (250 mg, 1,41 mmol) y 1-bromo-4-isotiocianatobenceno (302 mg, 1,41 mmol) en alcohol etílico a temperatura ambiente durante 18 h. Se cargó el balón con clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (EDCI) (405 mg, 2,12 mmol), y se agitó la mezcla durante 2 h antes de calentarse a reflujo hasta la mañana siguiente. Se dejó enfriar la reacción hasta ta y se concentró a presión reducida. Se disolvió el residuo en acetato de etilo y se lavó con solución acuosa 2N de ácido clorhídrico y agua, se secó (Na_2SO_4), y se concentró *al vacío*. Se purificó el residuo por cromatografía flash sobre gel de sílice, eluyendo con 85:15 hexanos/acetato de etilo para suministrar el compuesto del título (315 mg, 62%). CL-EM *m/z* 357,1 (MH^+), tiempo de retención 4,20 minutos.

Intermediario OO

N-(4-Bromo-2-fluorofenil)-5-(trifluorometil)-1,3-benzoxazol-2-amina



Se agitaron 2-Amino-4-(trifluorometil)fenol (580 mg, 3,25 mmol) y 4-bromo-2-fluoro-1-isotiocianatobenceno (750 mg, 3,25 mmol) en alcohol etílico a temperatura

~~295~~
295

ambiente durante 18 h. Se cargó el balón con clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (EDCI) (405 mg, 2,12 mmol), y se agitó la mezcla durante 2 h antes de calentarse a reflujo hasta la mañana siguiente. Se dejó enfriar la reacción hasta ta y se concentró a presión reducida. Se disolvió el residuo en acetato de etilo y se lavó con solución acuosa 2N de ácido clorhídrico y agua, se secó (Na_2SO_4), y se concentró *al vacío*. El material en bruto se suspendió en éter, se sonicó, y se recolectó el sólido resultante por filtración para suministrar el compuesto del título (214 mg, 18%). CL-EM *m/z* 375,1 (MH^+), tiempo de retención 3,70 minutos.

De un modo similar a los procedimientos descritos con anterioridad, se prepararon las siguientes *N*-(4-bromofenil)-*N*-(1,3-benzoxazol-2-il)aminas a partir de 4-bromo-1-isotiocianatobenceno y 2-aminofenol apropiados:

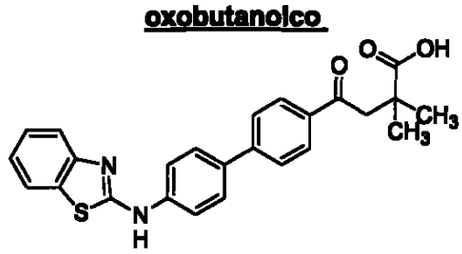
(a) *N*-(4-bromo-2-fluorofenil)-*N*-(5-metil-1,3-benzoxazol-2-il)amina
(CL-EM *m/z* 321,2 (MH^+), tiempo de ret. 3,69 min);

(b) *N*-(4-bromofenil)-*N*-(6-metil-1,3-benzoxazol-2-il)amina
(CL-EM *m/z* 303,2 (MH^+), tiempo de ret. 3,49 min).

Preparación de los Compuestos de Fórmula (I)

Ejemplo 1

Ácido 4-[4'-(1,3-Benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoico



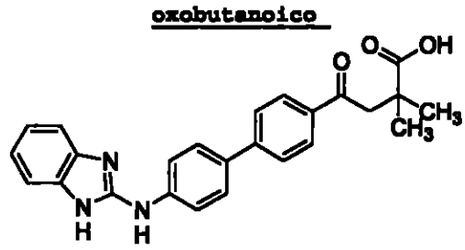
En un vial de 8 ml con tapa a rosca, se calentó una mezcla de 4-(4'-amino-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo (60 mg, 0,19 mmol) y 2-cloro-1,3-benzotiazol (40 mg, 0,23 mmol) en 3 ml n-butanol a 90°C hasta la mañana siguiente. La formación de 4-[4'-(1,3-

~~296~~
296

benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoato de metilo se monitoreó por CL-EM. Se eliminó el solvente a presión reducida. Se disolvió el residuo en 2 ml tetrahidrofurano/dioxano (1:1), y se agregó 3 equivalentes de hidróxido de sodio acuoso 1 N a la solución. Se agitó la mezcla a t.a. hasta la mañana siguiente y luego a 50°C durante 2 h. El progreso de la reacción de hidrólisis se monitoreó por CL-EM. Una solución de HCl acuoso 1N (3,1 equivalentes) luego se agregó a la mezcla, y se eliminó el solvente a presión reducida. Se disolvió el residuo nuevamente en 2 ml metanol y una cantidad mínima de DMF, y el producto se aisló y se purificó por HPLC preparativa de fase inversa (Gradiente agua/ acetonitrilo, que contenía 0,1% de TFA) para dar 40 mg de ácido 4-[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoico (Rendimiento: 45%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 11,90 (bs, 1 H), 10,65 (s, 1 H), 8,00 (d, 2 H), 7,90 (d, 2 H), 7,80 (m, 5 H), 7,60 (d, 1 H), 7,35 (t, 1 H), 7,20 (t, 1 H), 3,30 (s, 2 H), 1,10 (s, 6 H); CL-EM *m/z* 431,2 (MH^+), tiempo de ret. 3,40 min.

Ejemplo 2

Ácido 4-[4'-(1H-Bencimidazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoico



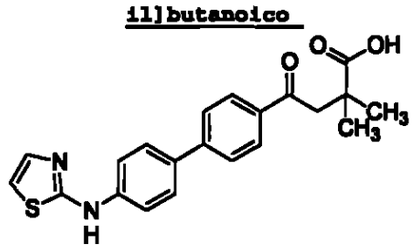
Este compuesto se preparó a partir de 4-(4'-amino-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo (64 mg, 0,21 mmol) y 2-cloro-1H-benzoimidazol (37,6 mg, 0,25 mmol) de un modo similar al método descrito para el ácido 4-[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoico, dando 40,7 mg (48%) del producto deseado. ^{1}H RMN

297.
297

(400 MHz, DMSO-d_6) δ 12,00 (br s, 1 H), 11,05 (br s, 1 H), 8,05 (d, 2 H), 7,85 (m, 4 H), 7,65 (d, 2 H), 7,40 (m, 2 H), 7,10 (m, 2 H), 3,35 (s, 2 H), 1,25 (s, 6 H). CL-EM m/z 414,3 (MH^+), tiempo de ret. 2,27 min.

Ejemplo 3

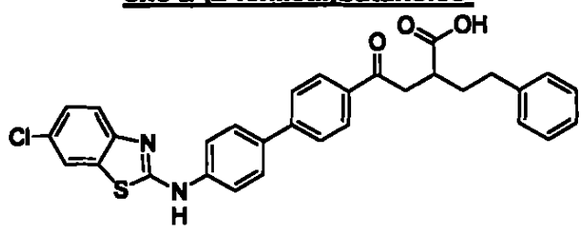
Ácido 2,2-Dimetil-4-oxo-4-[4'-(1,3-tiazol-2-ilamino)-1,1'-bifenil-4-il]butanoico



Este compuesto se preparó a partir de 4-(4'-amino-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo (64 mg, 0,21 mmol) y 2-bromotiazol (41 mg, 0,25 mmol) de un modo similar al método descrito para el ácido 4-[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoico, dando 18,6 mg (24%) del producto deseado. CL-EM m/z 381,4 (MH^+), tiempo de ret. 2,53 min.

Ejemplo 4

Ácido 4-[4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il]-4-oxo-2-(2-feniletil)butanoico



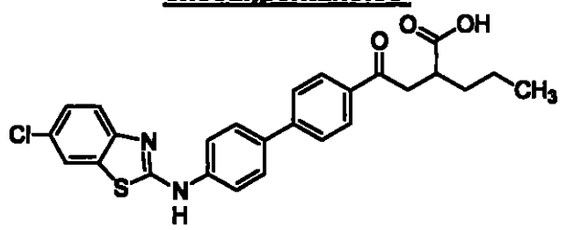
Este compuesto se preparó a partir de 4-(4'-amino-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato de metilo (78 mg, 0,20 mmol), 2,6-dicloro-1,3-benzotiazol (61,6 mg, 0,30 mmol) de un modo similar al método descrito para el ácido 4-[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoico, dando 26,7 mg (25%) del producto deseado.

298

^{1}H RMN (400 MHz, DMSO-d_6) δ 10,80 (br s, 1 H), 7,75-8,05 (m, 9 H), 7,60 (d, 1 H), 7,10-7,40 (m, 6 H), 3,50 (q, 1 H), 3,10 (m, 1 H), 2,85 (m, 1 H), 2,65 (m, 2 H), 1,80 (m, 2 H). CL-EM *m/z* 541,3 (MH^+), tiempo de ret. 4,07 min.

Ejemplo 5

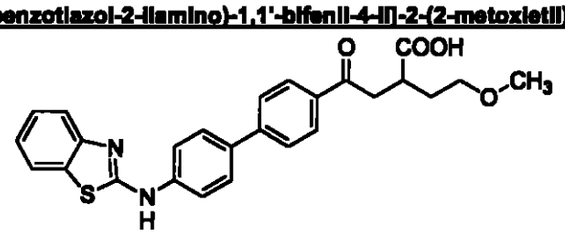
Ácido 2-(2-(4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2-oxoetil)pentanoico



Este compuesto se preparó a partir de 2-[2-(4'-amino-1,1'-bifenil-4-il)-2-oxoetil]pentanoato de metilo (68 mg, 0,20 mmol) y 2,6-dicloro-1,3-benzotiazol (61,3 mg, 0,30 mmol) de un modo similar al método descrito para el ácido 4-[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoico, dando 17,2 mg (18%) del producto deseado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 12,10 (br s, 1 H), 10,75 (br s, 1 H), 7,75-8,05 (m, 9 H), 7,60 (d, 1 H), 7,35 (m, 1 H), 3,40 (q, 1 H), 3,10 (m, 1 H), 1,55 (m, 2 H), 1,35 (m, 2 H), 0,85 (t, 3 H). CL-EM *m/z* 479,3 (MH^+), tiempo de ret. 3,88 min.

Ejemplo 6

Ácido 4-[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2-(2-metoxietil)-4-oxobutanoico



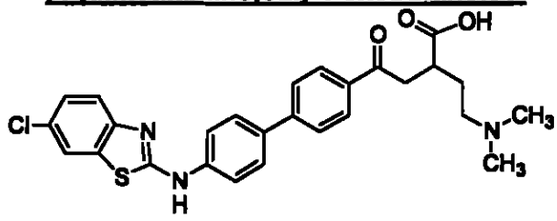
A una solución de 4-(4'-amino-1,1'-bifenil-4-il)-2-(2-metoxietil)-4-oxobutanoato de etilo (75 mg, 0,21 mmol) en butanol (4 ml), se agregó 2-cloro-benzotiazol (43 mg, 0,25 mmol) y se calentó la

~~299~~
299

mezcla de reacción a 90°C hasta la mañana siguiente. Se eliminó el solvente por evaporación rotativa, se disolvió el residuo nuevamente en DMF (1 ml), se agregó una solución acuosa 1 N de NaOH (0,63 ml, 0,63 mmol), y se agitó la mezcla a t.a. hasta la mañana siguiente. Se agregó una solución de HCl acuoso 1 N (0,3 ml, 0,3 mmol) y metanol (5 ml) a la mezcla de reacción, y se purificó el producto en bruto por HPLC preparativa de fase inversa (Gradiente agua/ acetonitrilo, que contenía 0,1% de TFA) para producir ácido 4-[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2-(2-metoxietil)-4-oxobutanoico como un sólido blanco (30 mg, 31%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,05 (d, 2 H), 7,95 (d, 2 H), 7,70 (m, 5 H), 7,60 (d, 1 H), 7,30 (t, 1 H), 7,15 (t, 2 H), 3,35 (m, 2 H), 3,25 (s, 3 H), 3,20 (m, 2 H), 2,90 (m, 1 H), 1,95-1,75 (m, 2 H); Tiempo de retención de CL-EM 3,29 min (método 2), *m/z* 461,15 (MH^+).

Ejemplo 7

Ácido 4-(4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il)-2-[2-(dimetilamino)etil]-4-oxobutanoico



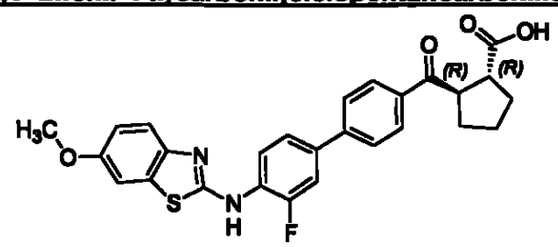
Este compuesto se preparó a partir de 4-(4'-amino-1,1'-bifenil-4-il)-2-[2-(dimetilamino)etil]-4-oxobutanoato de metilo (60 mg, 0,17 mmol) y 2,6-dicloro-1,3-benzotiazol (51,8 mg, 0,25 mmol) de un modo similar al método descrito para el ácido 4-[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoico, suministrando 14,1 mg (13%) del producto deseado como la sal de trifluoroacetato. ^{1}H RMN (400 MHz, CD_3OD) δ 8,10 (d, 2 H), 7,70-8,10 (m, 8 H), 7,30 (m, 1 H), 3,60 (m, 1 H), 3,30-3,40 (m, 3 H), 3,10 (m, 1 H), 2,95 (s, 6 H), 2,20 (m, 1 H), 2,00 (m, 1 H). CL-EM *m/z* 508,1 (MH^+), tiempo de ret. 2,66 min.

Ejemplo 8

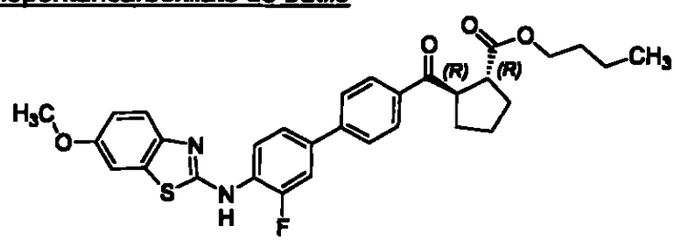
Ácido (1*R*,2*R*)-2-({3'-Fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-

300.

1,1'-bifenil-4-il)carbonil)ciclopentancarboxílico



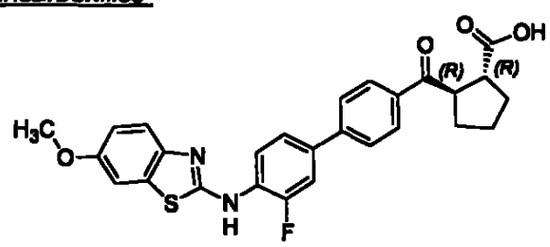
(1*R*,2*R*)-2-({3'-fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxilato de butilo



Paso 1. Se disolvió (1*R*,2*R*)-2-[(4'-amino-3'-fluoro-1,1'-bifenil-4-il)carbonil]-ciclopentancarboxilato de metilo (462 mg, 1,35 mmol) en n-butanol (15 ml), y se agregaron 6-metoxi-2-(metilsulfonil)-1,3-benzotiazol (162 mg, 0,8 mmol) y HCl acuoso 4 M (1,5 ml). Se calentó la mezcla a 90°C durante 5 h. Se agregó una porción adicional de 6-metoxi-2-(metilsulfonil)-1,3-benzotiazol (162 mg, 0,8 mmol), y se agitó la mezcla hasta la mañana siguiente a 90°C. Luego se eliminó el solvente por evaporación rotativa, y se purificó el residuo por cromatografía flash (Biotage Flash 40 M, hexano/EtOAc 3:1) para producir (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-carbonil)ciclopentancarboxilato de butilo (480 mg, 65%). Tiempo de retención de CL-EM 4,36 min, *m/z* 547,3 (MH^+); ^1H RMN (300 MHz, $CDCl_3$) δ: 0,85 (t, 3H), 1,25-1,35 (m, 2H), 1,40-1,58 (m, 2H), 1,74-1,84 (m, 3H), 1,91-1,96 (m, 1H), 2,11-2,20 (m, 2H), 3,40-3,46 (m, 1H), 3,84 (s, 3H), 4,03 (t, 2H), 6,81-6,87 (m, 1H), 6,98 (dd, 1H), 7,18 (d, 1H), 7,40-7,52 (m, 2H), 7,64 (d, 2H), 8,14 (d, 2H), 8,42 (t, 1H).

301

Ácido (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-carbonil)ciclopentancarboxílico



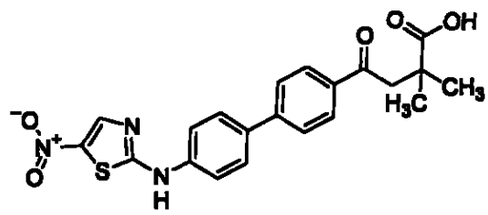
Paso 2. A una solución de (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxilato de butilo en metanol (8 ml) se agregó hidróxido de sodio acuoso 1 N (6,15 ml), y se agitó la mezcla a 50°C hasta la mañana siguiente. Luego se eliminó el solvente por evaporación rotativa. Se agregó agua (5 ml) al residuo, y se extrajo la mezcla con acetato de etilo. Luego se trató la fase acuosa con HCl acuoso 1 N para ajustar la acidez hasta un pH 2, y luego se extrajo con acetato de etilo. Se evaporó la fase orgánica a presión reducida, y se purificó el residuo por cromatografía flash (Biotage Flash 40S, EtOAc/hexano 6:1) para producir ácido (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico (129 mg, 30%, 89% de ee). Tiempo de retención de CL-EM 3,56 min, *m/z* 491,3 (MH^+); ^{1}H RMN (300 MHz, DMSO-d_6) δ 1,58-1,84 (m, 4H), 1,96-2,01 (m, 1H), 2,14-2,17 (m, 1H). 3,22 (q, 1H), 3,77 (s, 3H), 4,02-4,10 (q, 1H), 6,94 (dd, 1H), 7,46 (d, 1H), 7,53 (d, 1H), 7,65-7,76 (m, 2H), 7,86 (d, 2H), 8,04 (d, 2H), 8,72 (t, 1H), 10,33 (br s, 1H).

Ejemplo 9

Ácido 2,2-dimetil-4-[4'-[(5-nitro-1,3-tiazol-2-il)amino]-1,1'-bifenil-4-il]-4-oxobutanoico

302

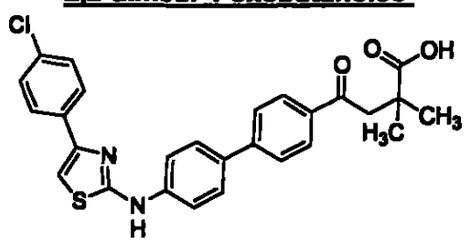
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En un vial de 8 ml con tapa a rosca, se calentó una mezcla de ácido 4-(4'-amino-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoico (60 mg, 0,20 mmol) y 2-bromo-5-nitro-1,3-tiazol (63,3 mg, 0,30 mmol) en 4 ml de n-butanol a 90°C hasta la mañana siguiente. Se eliminó el solvente a presión reducida. La mezcla se disolvió en 5 ml de MeOH/DMF 1:4 y se purificó por HPLC de fase reversa para suministrar 8,9 mg (10%) del producto deseado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 11,55 (br s, 1 H), 8,50 (s, 11 H), 7,70-8,05 (m, 8 H), 3,15 (d, 1 H), 1,25 (s, 6 H); CL-EM *m/z* 426,2 (MH^+), tiempo de ret. 3,12 min.

Ejemplo 10

Ácido 4-(4'-{[4-(4-clorofenil)-1,3-tiazol-2-il]amino}-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoico



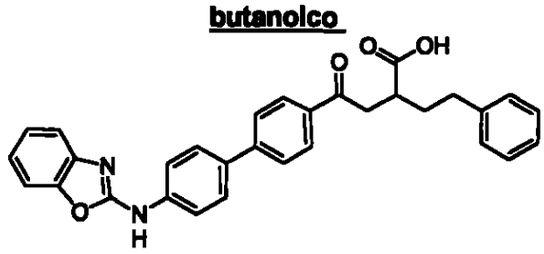
En un vial de 8 ml con tapa a rosca, una mezcla de ácido 4-(4'-amino-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoico (60 mg, 0,20 mmol) y tiocianato de 2-(4-clorofenil)-2-oxoetilo (64 mg, 0,30 mmol) en 4 ml de n-butanol se calentó a 90°C hasta la mañana siguiente. Se eliminó el solvente a presión reducida. La mezcla se disolvió en 5 ml de MeOH/DMF a 1:4 y se purificó por HPLC de fase inversa para suministrar 6,8 mg (7%) del producto deseado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 11,90 (br s, 1 H),

303.

10,50 (s, 1 H), 7,75-8,00 (m, 10 H), 7,50 (m, 3 H), 3,30 (m, 2 H), 1,05 (s, 6 H); CL-EM m/z 491,2 (MH^+), tiempo de ret. 3,83 min.

Ejemplo 11

Ácido 4-[4'-(1,3-Benzoxazol-2-ilamino)-1,1'-bifenil-4-il]-4-oxo-2-(2-feniletil)-butanoico

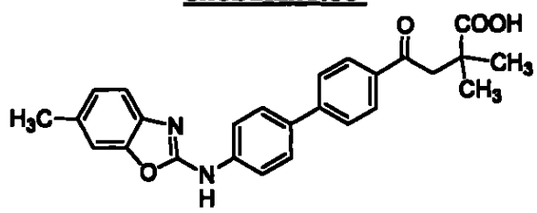


Una solución de 4-(4'-amino-1,1'-bifenil-4-il)-4-oxo-2-(2-feniletil)butanoato de etilo (100 mg, 0,25 mmol) y 2-clorobenzoxazol (38,3 mg, 0,25 mmol) en tolueno (1,0 ml) se calentó a reflujo durante 16 h. Se eliminó el solvente a presión reducida, y se disolvió el residuo en diclorometano. Se lavó la solución con agua, se eliminó nuevamente el solvente a presión reducida, y se disolvió el residuo en metanol (1 ml) y tetrahidrofurano (1 ml). Se agregó una solución acuosa 1 N de hidróxido de sodio (0,77 ml, 0,77 mmol), y se agitó la mezcla a t.a. durante 16 h y luego se concentró a presión reducida. Se purificó el residuo por HPLC preparativa de fase inversa (gradiente agua/acetonitrilo, que contenía 0,1% de TFA) para producir ácido 4-[4'-(1,3-benzoxazol-2-ilamino)-1,1'-bifenil-4-il]-4-oxo-2-(2-feniletil)butanoico (40 mg, 33% de rendimiento). Tiempo de retención de CL-EM 4,14 min, m/z 519,5 (MH^+); ^1H RMN (300 MHz, DMSO-d_6) δ 1,82-1,90 (m, 2H), 2,68 (m, 2H), 2,80-2,85 (m, 1H), 3,16 (dd, 1H), 3,41 (m, 1H), 7,10-7,30 (m, 8H), 7,48 (t, 2H), 7,78-7,86 (m, 4H), 7,89 (d, 2H), 8,02 (d, 2H), 10,83 (br s, 1H).

Ejemplo 12

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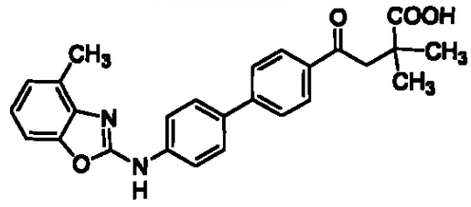
Ácido 2,2-dimetil-4-{4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico



A una solución de 4-(4'-amino-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo (74 mg, 0,24 mmol) en dicloroetano (3 ml), se agregó 6-metil-2-(metilsulfonil)-1,3-benzoxazol (50 mg, 0,24 mmol), y se calentó la mezcla a 85°C hasta la mañana siguiente. Se eliminó el solvente por evaporación rotativa, y se disolvió el residuo nuevamente en DMF (5 ml). Se agregó una solución acuosa 1 N de NaOH (0,72 ml, 0,72 mmol), y se calentó la mezcla a 65°C hasta la mañana siguiente. Se agregaron una solución de HCl acuoso 1 N (0,24 ml, 0,24 mmol) y metanol (5 ml) a la mezcla de reacción y se purificó el producto en bruto por HPLC preparativa de fase reversa (gradiente agua/acetonitrilo, que contenía 0,1% de TFA) para producir ácido 2,2-dimetil-4-{4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico como un sólido blanco (32,6 mg, 32,1 %). ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,00 – 7,50 (m, 8 H), 7,30 (d, 2 H), 7,05 (d, 1 H), 3,30 (s, 2 H), 2,50 (s, 3 H), 1,10 (s, 6 H); Tiempo de retención de CL-EM 3,53 min (método 2), *m/z* 429,17 (MH^+).

Ejemplo 13

Ácido 2,2-Dimetil-4-{4'-[(4-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico

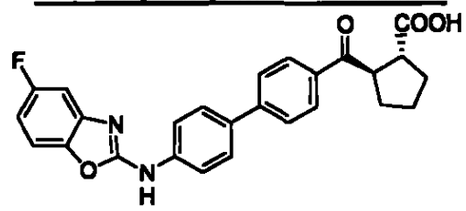


A una solución de 4-(4'-amino-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoato de metilo (74 mg, 0,24 mmol) en dicloroetano (3 ml), se agregó 4-metil-2-(metilsulfonil)-1,3-benzoxazol (50 mg, 0,24 mmol), y se calentó la mezcla a 85°C hasta la mañana siguiente. Se eliminó el solvente por

evaporación rotativa y se disolvió el residuo nuevamente en DMF (5 ml). Se agregó una solución acuosa 1 N de NaOH (0,72 ml, 0,72 mmol), y se calentó la mezcla a 65°C hasta la mañana siguiente. Se agregó una solución de HCl acuoso 1 N (0,24 ml, 0,24 mmol) y metanol (5 ml) a la mezcla de reacción y se purificó el producto en bruto por HPLC preparativa de fase inversa (Gradiente agua/ acetonitrilo, que contenía 0,1% de TFA) para producir ácido 2,2-dimetil-4-{4'-[(4-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico como un sólido blanco (32,6 mg, 32,1%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,00-7,80 (m, 8 H), 7,30 (d, 1 H), 7,05 (d, 2 H), 3,30 (s, 2 H), 2,50 (s, 3 H), 1,10 (s, 6 H); Tiempo de retención de CL-EM 3,77 min (método 2), *m/z* 429,2 (MH^+).

Ejemplo 14

Ácido *trans*-2-{[4'-[(5-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il] carbonil}ciclopentancarboxílico

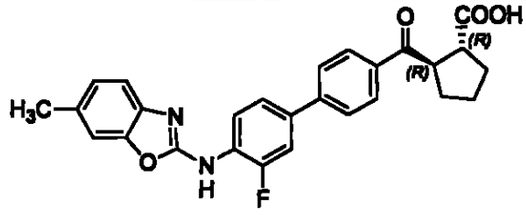


A una solución de *trans*-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxilato de metilo (100 mg, 0,31 mmol) en dicloroetano (3 ml), se agregó 5-fluoro-2-(metilsulfonil)-1,3-benzoxazol (80 mg, 0,37 mmol) y se calentó la mezcla a 85°C hasta la mañana siguiente. Se eliminó el solvente por evaporación rotativa, y se disolvió el residuo nuevamente en DMF (5 ml). Se agregó una solución acuosa 1 N de NaOH (0,93 ml, 0,93 mmol) y se calentó la mezcla a 65°C hasta la mañana siguiente. Se agregaron una solución de HCl acuoso 1 N (0,31 ml, 0,31 mmol) y metanol (5 ml) a la mezcla de reacción, y se purificó el producto en bruto por HPLC preparativa de fase inversa (Gradiente agua/ acetonitrilo, que contenía 0,1% de TFA) para producir ácido 2-({4'-[(5-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico como un sólido blanco (43,7 mg, 31,4%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,05 (d, 2 H), 7,90-7,80 (m, 6 H), 7,50 (m, 1 H), 7,30 (m, 1 H), 6,95 (m, 1 H), 4,05 (m, 1 H), 3,20 (m, 1 H), 2,20 (m, 1 H), 1,95 (m, 1 H), 1,80-1,60 (m, 4 H); Tiempo de retención de CL-EM 3,66 min (método 2), *m/z* 445,1 (MH^+).

306.

Ejemplo 15

Ácido (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico



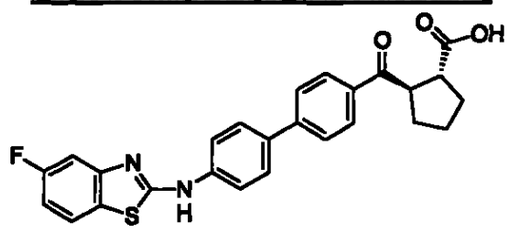
A una solución de (1*R*,2*R*)-2-[(4'-amino-3'-fluoro-1,1'-bifenil-4-il)carbonil]-ciclopentancarboxilato de metilo (800 mg, 2,34 mmol, 78% de ee) en diclorotano (15 ml), se agregó 6-metil-2-(metilsulfonil)-1,3-benzoxazol (891 mg, 4,22 mmol), y se calentó la mezcla a 85°C hasta la mañana siguiente. Se eliminó el solvente por evaporación rotativa, y se purificó el residuo mediante el uso de un sistema de cromatografía flash Biotage QuadUV (eluyente: hexano/EtOAc 80:20) para dar (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-carbonil)ciclopentancarboxilato de metilo (472 mg). Se disolvió nuevamente este éster intermediario en dioxano/THF 1:1 (20 ml), se agregó una solución acuosa 1 N de NaOH (7,02 ml, 7,02 mol), y se calentó la mezcla a 50°C hasta la mañana siguiente. Se eliminó el solvente por evaporación rotativa, y se agregaron agua (20 ml) y EtOAc (40 ml) al residuo. Se separó la fase acuosa, se acidificó hasta un pH 5 con el agregado de HCl acuoso 1 N, y luego se extrajo con EtOAc (2 x 60 ml). Se lavaron las fases orgánicas combinadas con NaCl saturado y se secaron (Na_2SO_4). Se eliminó el solvente por evaporación rotativa y se disolvió el residuo nuevamente en DMF (10 ml) y metanol (20 ml). Se purificó el producto en bruto por HPLC preparativa de fase reversa (gradiente agua/acetonitrilo, que contenía 0,1% de TFA) para producir ácido (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico como un sólido blancuzco (161 mg, 15% de rendimiento, 80% de ee). ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,40 (m, 1 H), 8,00-7,60 (m, 6 H), 7,30 (d, 2 H), 7,00 (d, 1 H), 4,05 (m, 1 H), 3,20 (m, 1 H), 2,40 (s, 3 H), 2,20 (m, 1 H), 1,95 (m, 1 H), 1,80-1,60 (m, 4 H); Tiempo de retención de CL-EM 3,57 min, *m/z* 459,3 (MH^+).

Ejemplo 16

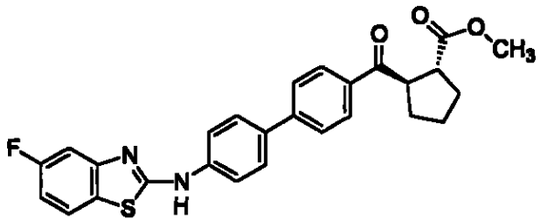
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Ácido *trans*-2-({4'-[(5-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico

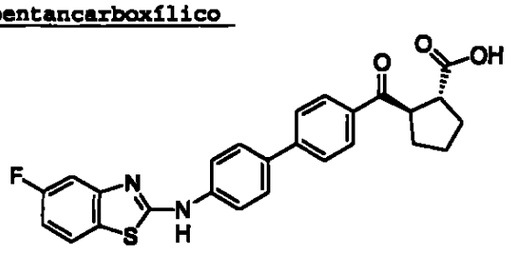


***trans*-2-({4'-[(5-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxilato de metilo**



Paso 1. Se combinaron 2-cloro-5-fluoro-1,3-benzotiazol (29 mg, 0,16 mmol) y *trans*-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclopentancarboxilato de metilo (50 mg, 0,16 mmol) en 1-butanol. La solución se trató con HCl 4 M en dioxano (4 µl, 0,016 mmol) y se calentó a 90°C durante 18 h. Se concentró la mezcla de reacción a presión reducida. Se suspendió el residuo en metanol, y se recolectó el sólido resultante por filtración y se secó *al vacío*. El compuesto del título se obtuvo como un sólido amarillo pálido (55 mg, 77 %); CL-EM *m/z* 475,3 (MH^+), tiempo de retención 3,97 minutos.

Ácido *trans*-2-({4'-[(5-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico

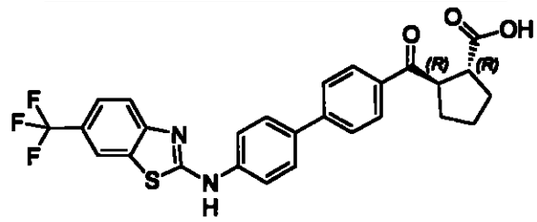


308

Paso 2. Se agregó una solución acuosa de hidróxido de sodio 1N (1 ml) a 2-({4'-[(5-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)-ciclopentancarboxilato de *trans*-metilo (55 mg, 0,12 mmol) en THF (2 ml). Se agregó metanol hasta que la mezcla se tornó homogénea, y se calentó la solución resultante a 60°C durante 1 h. Se concentró la reacción a presión reducida para eliminar el exceso de solventes, y se repartió el residuo entre agua y cloroformo/isopropanol (4:1). Se ajustó la fase acuosa hasta un pH 2 con el agregado de solución acuosa de ácido fosfórico, con agitación. Luego se separó la fase orgánica, se secó (Na_2SO_4), y se concentró a presión reducida. Se suspendió el residuo en acetona, y se recolectó el sólido resultante por filtración y se secó *al vacío* para suministrar el compuesto del título (45 mg, 84%). ^{1}H RMN (300 MHz, acetona-d_6) δ 10,40–10,10 (br s, 1 H), 8,15 (d, 2 H), 8,01 (d, 2 H), 7,87–7,82 (m, 5 H), 7,41 (dd, 1 H), 7,05-6,95 (m, 1 H), 4,26–4,17 (m, 1 H), 3,43-3,34 (m, 1 H), 2,31–2,23 (m, 1 H), 1,98–1,70 (m, 5 H); CL-EM *m/z* 461,3 (MH^+), tiempo de retención 3,56 minutos.

Ejemplo 17

Ácido (1*R*,2*R*)-2-[(4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentancarboxílico



Se diluyó una mezcla de (1*R*,2*R*)-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclopentancarboxilato de metilo (150 mg, 0,464 mmol) y 2-cloro-6-(trifluorometil)-1,3-benzotiazol (132 mg, 0,557 mmol) con *n*-butanol (3 ml) y se trató con una cantidad catalítica de HCl 4 M en dioxano. Se calentó la suspensión a 90°C hasta la mañana siguiente. Se concentró la mezcla de reacción a presión reducida y se purificó por

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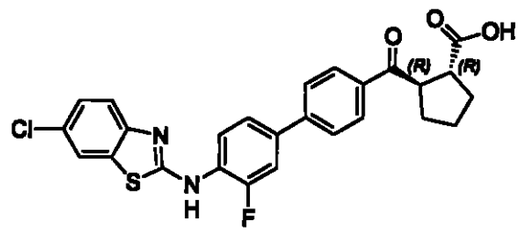
cromatografía flash sobre gel de sílice, eluyendo con un gradiente de hexanos/acetato de etilo 9:1 a 3:2. el producto deseado se suspendió en dietil éter, y se recolectó el sólido resultante por filtración y se lavó con dietil éter adicional y hexanos. CL-EM para el n-butil éster: CL-EM *m/z* 567,3 (MH^+), 4,67 min; ^1H RMN (300 MHz, $CDCl_3$) δ 8,14-8,10 (m, 3 H), 7,80-7,71 (m, 6 H), 7,62 (d, 2 H), 4,17-4,13 (m, 1 H), 4,09-4,04 (m,2 H), 3,51-3,41 (m, 1 H), 2,21-2,13 (m, 2 H), 1,97-1,90 (m, 1 H), 1,81-1,78 (m, 3 H), 1,58-1,51 (m, 2 H), 1,35-1,28 (m, 2 H),1,23-1,18 (t, 3 H), 0,88 (t, 2 H). El sólido blancuzco se diluyó con metanol (2 ml) y tetrahidrofurano (2 ml) y se trató con solución acuosa 2 M de hidróxido de sodio (2 ml). Se agitó la solución hasta la mañana siguiente a ta. Se acidificó la mezcla con el agregado de un exceso de solución acuosa 2 M de ácido clorhídrico. Se extrajo la solución de ácido con acetato de etilo. La fase orgánica se combinó, se secó ($MgSO_4$), y se concentró a presión reducida. Se suspendió el residuo en metanol y los sólidos resultantes se eliminaron por filtración. El filtrado, que contenía el producto, se concentró a presión reducida para dar el compuesto del título como un sólido naranja pálido (30 mg, 13% de rendimiento general). ^1H RMN (tetrahidrofurano-d_8) δ 10,85 (s, 1 H), 8,11-8,07 (m, 3 H), 7,96-7,91 (m, 2 H), 7,79-7,71 (m, 5 H), 7,63-7,59 (dd, 1 H), 4,18 (q, 1 H), 3,37 (q, 1 H), 2,2-1,77 (m, 6 H); CL-EM *m/z* 511,3 (MH^+), tiempo de retención 4,27 minutos.

Ejemplo 18

Ácido (1*R*,2*R*)-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico

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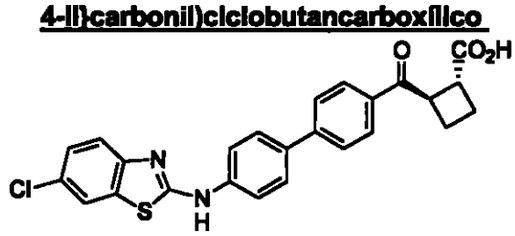
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Una suspensión de *N*-(4-yodo-2-fluorofenil)-6-cloro-1,3-benzotiazol-2-amina (200 mg, 0,49 mmol), bis(pinacolato)diboro (130 mg, 0,52 mmol), KOAc (150 mg, 1,48 mmol), y $PdCl_2$(dppf) (30 mg, 0,04 mmol) en DMF (5,0 ml) se desgasificó burbujeando un flujo de nitrógeno durante 30 minutos. La mezcla de reacción se calentó bajo nitrógeno a 85°C durante 3 h. Luego de enfriar la mezcla hasta la ta, se agregaron ácido (1*R*,2*R*)-2-(4-bromobenzoil)ciclopentancarboxílico (140 mg, 0,49 mmol, >99% de ee), Cs_2CO_3 (400 mg, 1,23 mmol) y $PdCl_2$(dppf) (30 mg, 0,04 mmol), y se calentó la mezcla de reacción a 85°C bajo nitrógeno durante 3 h. El análisis de TLC poco material de partida restante. Se enfrió la mezcla de reacción hasta ta, y se diluyó con agua (50 ml). Luego de filtrar la mezcla a través de un taco de Celite®, se agregó HCl 1 N al filtrado para ajustar la acidez hasta un pH<3. El sólido que se formó se recolectó por filtración, luego se disolvió en EtOAc (50 ml), y se secó la solución resultante sobre Na_2SO_4. La eliminación del solvente y el secado *al vacío* dieron el producto deseado (120 mg, 60%, >99% de ee). CL-EM *m/z* 495,3 (MH^+), tiempo de retención 4,01 min.

Ejemplo 19

Ácido *trans*-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclobutancarboxílico

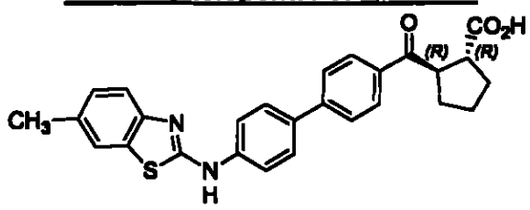


311

A una solución de *trans*-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclobutan-carboxilato de metilo (100 mg, 0,32 mmol) en n-butanol (15 ml) se agregó 2,6-dicloro-1,3-benzotiazol (396 mg, 1,94 mmol), y se calentó la mezcla de reacción resultante a 90°C hasta la mañana siguiente. La mezcla se evaporó hasta la sequedad y el residuo se absorbió en MeOH. Luego NaOH acuoso 1 N (1,0 ml, 1,0 mmol) se agregó a la suspensión, y se agitó la mezcla de reacción a 50°C hasta la mañana siguiente. Se concentró la mezcla de reacción, y se suspendió el residuo en agua. Se agregó HCl concentrado para ajustar la acidez hasta un pH 1, y el precipitado que se formó se recolectó por filtración, se lavó con agua y MeOH, y se secó en estufa de vacío para dar ácido *trans*-2-({4'-[(6-cloro-1, 3-benzotiazol-2-il) amino]-1,1'-bifenil-4-il}carbonil)ciclobutancarboxílico (16 mg, 10%). Tiempo de retención de CL-EM 3,69; *m/z* 463,1 (MH^+); ^1H RMN (400 MHz, DMSO-d_6) δ 2,01-2,23 (m, 3H), 2,32 (m, 1H), 3,43 (m, 1H), 4,32 (m, 1H), 7,35 (m, 1H), 7,31 (m, 1H), 7,62 (d, 1H), 7,81 (m, 4H), 7,90 (d, 2H), 7,98 (m, 3H), 10,77 (s, 1H), 12,29 (s, 1H).

Ejemplo 20

Ácido *trans*-2-({4'-[(6-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclopentancarboxílico



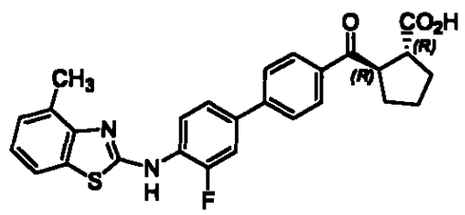
Se combinaron N-(4-yodofenil)-6-metil-1,3-benzotiazol-2-amina (0,28 g, 0,78 mmol) y *trans*-2-[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzoil]-ciclopentancarboxilato de metilo (0,25 g, 0,71 mmol) en un matraz seco bajo argón. Luego se agregaron tolueno (15 ml), EtOH (6 ml), y $NaHCO_3$ acuoso saturado (2 ml), y la solución resultante se desgasificó burbujeando una corriente de argón durante 30 minutos. Luego se agregó [1,1'-bis(difenilfosfin)-ferrocen]-dicloropaladio (II), en complejo con diclorometano (1:1) (57 mg, 0,07 mmol), y se

calentó la mezcla resultante a 85°C durante 16 h. Luego se diluyó la mezcla de reacción con EtOAc y se filtró a través de un taco de Celite®. Se eliminó el solvente por evaporación rotativa y el residuo se absorbió en MeOH. Luego se agregó NaOH acuoso 1 N (2,0 ml, 2,0 mmol) a la suspensión, y se agitó la mezcla de reacción a 50°C hasta la mañana siguiente. Se concentró la mezcla de reacción a presión reducida y se suspendió el residuo en agua. Se agregó HCl concentrado para ajustar la acidez hasta un pH 1, y se extrajo la suspensión con EtOAc. Se lavaron las fases orgánicas combinadas con salmuera, se secaron sobre sulfato de sodio, se pasaron a través de un taco de sílice gel, y se concentraron *al vacío*. El residuo se absorbió in EtOAc y se recolectó el precipitado por filtración, se lavó con EtOAc, MeOH, y DCM, y se secó en estufa de vacío para producir ácido *trans*-2-({4'-[(6-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico (0,24 g, 19%). Tiempo de retención de CL-EM 3,57; *m/z* 457,3 (MH^+); ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,57-1,86 (m, 4H), 2,00 (m, 1H), 2,17 (m, 1H), 2,37 (s, 3H), 3,22 (q, 1H), 4,08 (q, 1H), 7,14 (m, 1H), 7,51 (d, 1H), 7,61 (s, 1H), 7,80 (m, 3H), 7,89 (d, 2H), 8,05 (d, 2H), 10,58 (s, 1H), 12,19 (s, 1H).

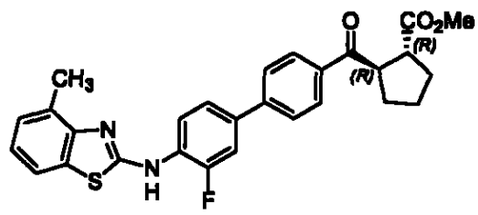
Ejemplo 21

Ácido (1*R*,2*R*)-2-({3'-fluoro-4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico

313

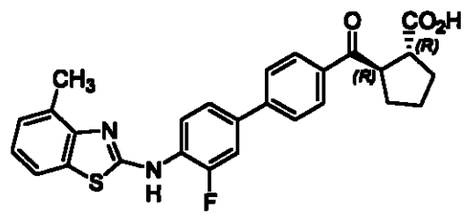


(R,R)-*trans*-2-({3'-fluoro-4'-[(4-metil-1, 3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-carbonil)ciclopentancarboxilato de metilo



Paso 1. Se combinaron N-(4-bromo-2-fluorofenil)-4-metil-1,3-benzotiazol-2-amina (0,10 g, 0,30 mmol) y (R,R)-*trans*-2-[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzoil]ciclopentancarboxilato de metilo (0,19 g, 0,54 mmol, 94% de ee) en un matraz seco bajo argón. Se agregaron tolueno (25 ml), EtOH (8 ml), y $NaHCO_3$ acuoso saturado (5 ml), y la suspensión resultante se desgasificó burbujeando con una corriente de argón durante 30 minutos. Luego se agregó [1,1'-bis(difenilfosfina)-ferroceno]dicloropaladio(II), en complejo con diclorometano (1:1) (40 mg, 0,05 mmol), y se calentó la mezcla resultante a 85°C durante 16 h. Luego se diluyó la mezcla de reacción con EtOAc y se separaron las fases. Se lavó la fase orgánica con acuoso HCl (1,0 M), agua y salmuera, se filtró, y se concentró *al vacío*. Se purificó el residuo por cromatografía flash (Biotage Flash 25S) usando 10 a 15% de acetato de etilo en hexano para producir (*R,R*)-*trans*-2-({3'-fluoro-4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxilato de metilo (0,09 g, 37%). ^1H RMN (400 MHz, CD_2Cl_2) δ 1,75-1,86 (m, 3H), 1,93 (m, 1H), 2,12-2,26 (m, 2H), 2,69 (s, 3H), 3,45 (q, 1H), 3,66 (s, 3H), 4,12 (q, 1H), 7,14 (t, 1H), 7,22 (d, 1H), 7,50 (m, 2H), 7,56 (t, 2H), 7,73 (d, 2H), 8,07 (d, 2H), 8,72 (t, 1H).

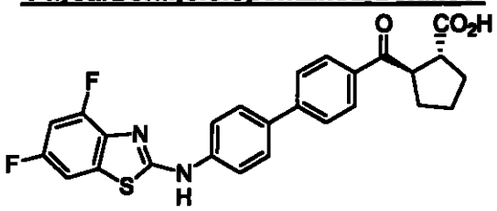
Ácido (*R,R*)-*trans*-2-({3'-fluoro-4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico



Paso 2. Se absorbió (*R,R*)-*trans*-2-({3'-fluoro-4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxilato de metilo (90 mg, 0,18 mmol) en MeOH. Luego se agregó NaOH acuoso 1 N (1,0 ml, 1,0 mmol) a la suspensión, y se agitó la mezcla de reacción a 50°C hasta la mañana siguiente. Se concentró la mezcla de reacción, y se suspendió el residuo en agua. Se agregó HCl conc. para ajustar la acidez hasta un pH 1, y se extrajo la mezcla con EtOAc. Se lavaron las fases orgánicas combinadas con salmuera, se secaron sobre sulfato de sodio, se filtraron y se concentraron para dar ácido (*R,R*)-*trans*-2-({3'-fluoro-4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico (32 mg, 36%). Tiempo de retención de CL-EM 3,97; *m/z* 475,3 (MH^+); ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,56-1,83 (m, 4H), 2,00 (m, 1H), 2,16(m, 1H), 2,57 (s, 3H), 3,22 (q, 1H), 4,09 (q, 1H), 7,07 (t, 1H), 7,16 (d, 1H), 7,63 (m, 1H), 7,70 (m, 1H), 7,75 (m, 1H), 7,88 (d, 2H), 8,05 (d, 2H), 8,84 (t, 1H), 10,47 (s, 1H).

Ejemplo 22

Ácido *trans*-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico



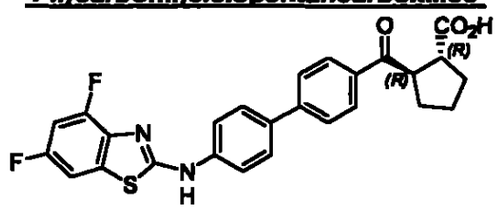
A una solución de *trans*-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclobutan-carboxilato de metilo racémico (250 mg, 0,77 mmol) en n-butanol (15 ml) se agregó 2-cloro-4,6-difluoro-1,3-benzotiazol (318 mg, 1,55 mmol), y se calentó la solución resultante a 90°C hasta la mañana siguiente. Luego se evaporó la mezcla hasta la

315

sequedad a presión reducida, y el residuo se absorbió en MeOH. Luego NaOH acuoso 1 N (8,0 ml, 8,0 mmol) se agregó a la suspensión, y se agitó la mezcla de reacción a 50°C hasta la mañana siguiente. Se concentró la mezcla de reacción a presión reducida, y se suspendió el residuo en agua. Se agregó HCl conc. para ajustar la acidez hasta un pH 1, y se extrajo la mezcla con EtOAc. Se lavaron las fases orgánicas combinadas con salmuera, se secaron sobre sulfato de sodio, se filtraron, y se concentraron. El residuo se absorbió en MeOH, y se recolectó el precipitado por filtración, se lavó con MeOH, EtOAc, y DCM, y se secó en estufa de vacío para producir ácido *trans*-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico racémico (160 mg, 43%). Tiempo de retención de CL-EM 4,12; *m/z* 479,3 (MH^+); ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,55-1,86 (m, 4H), 2,00 (m, 1H), 2,18 (m, 1H), 3,22 (q, 1H), 4,01 (q, 1H), 7,28 (m, 1H), 7,65 (m, 1H), 7,82 (m, 4H), 7,88 (d, 2H), 8,05 (d, 2H), 10,83(s, 1H), 12,23 (s, 1H).

Ejemplo 23

Ácido (1*R*,2*R*)-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico

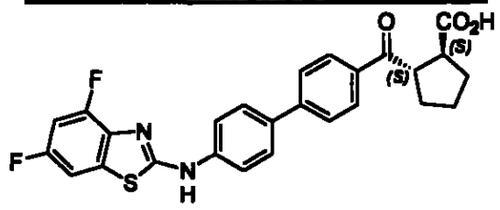


Se separó ácido *trans*-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il) amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico racémico (140 mg, 0,29 mmol) por HPLC quiral para producir ácido (1*R*,2*R*)-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico como el primer enantiómero eluyente (13,2 mg, 9%, 99% de ee). Tiempo de retención de CL-EM 3,64; *m/z* 479,2 (MH^+); ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,58-1,86 (m, 4H), 2,00 (m, 1H), 2,17 (m, 1H), 3,21 (q, 1H), 4,10 (q, 1H), 7,29 (m, 1H), 7,66 (m, 1H), 7,82 (m, 4H), 7,88 (d, 2H), 8,06 (d, 2H), 10,83 (s, 1H), 12,23 (s, 1H).

316.

Ejemplo 24

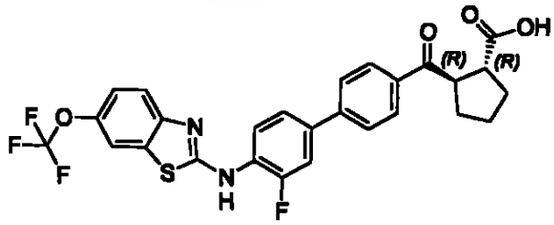
Ácido (1*S*,2*S*)-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico



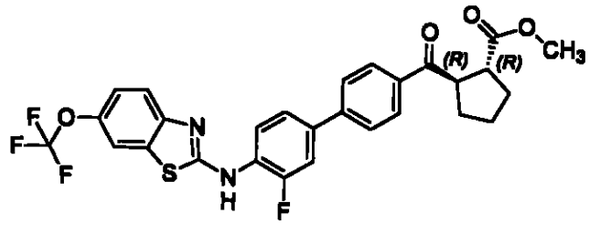
Se separó ácido *trans*-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico racémico (140 mg, 0,29 mmol) por HPLC quiral para producir ácido (1*S*,2*S*)-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico como segundo enantiómero en eluir (23,8 mg, 17%, 74% de ee). Tiempo de retención de CL-EM 3,65; *m/z* 479,2 (MH^+); ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,56-1,87 (m, 4H), 2,01 (m, 1H), 2,18 (m, 1H), 3,22 (q, 1H), 4,09 (q, 1H), 7,28 (m, 1H), 7,66 (m, 1H), 7,82 (m, 4H), 7,89 (d, 2H), 8,06 (d, 2H), 10,83 (s, 1H), 12,22 (s, 1H).

Ejemplo 25

Ácido (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-trifluorometoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico



(1*R*,2*R*)-2-[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentancarboxilato de metilo



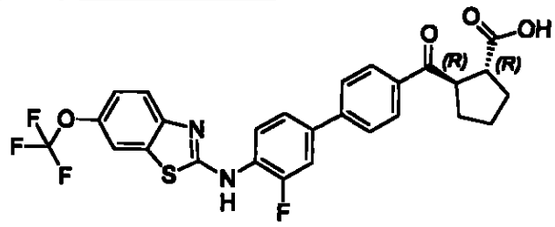
317

Paso 1. En un balón de 3 bocas de 100 ml, una mezcla de (1*R*,2*R*)-2-(4-bromobenzoil)ciclopentancarboxilato de metilo (3,11 g, 10 mmol, 94,5% de ee), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi-1,3,2-dioxaborolano (2,54 g, 10 mmol), y acetato de potasio (2,94 g, 30 mmol) en 50 ml *N*,*N*-dimetilformamida se desgasificó burbujeando una corriente de nitrógeno gaseoso 30 minutos. Se agregó acetato de paladio (II) (0,07 g, 0,30 mmol) a la mezcla de reacción, y se calentó la mezcla a 85°C durante 3 h. La transformación de (1*R*,2*R*)-2-(4-bromobenzoil)ciclopentan-carboxilato de metilo a (1*R*,2*R*)-2-[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-benzoil]ciclopentancarboxilato de metilo se confirmó por análisis de TLC. Se enfrió la mezcla hasta la ta y se vertió en una ampolla de decantación. Se agregaron acetato de etilo (100 ml) y H_2O (100 ml). Se lavó la fase orgánica con agua (2 x 50 ml) y se trató con Na_2SO_4 y carbón activado. Se filtró la mezcla a través de un taco de sílice gel, y se concentró el filtrado a presión reducida para dar (1*R*,2*R*)-2-[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzoil]ciclopentancarboxilato de metilo como un aceite. Se transfirió este aceite a un balón de 3 bocas de 250 ml. Al balón, se agregaron *N*-(4-bromo-2-fluorofenil)-*N*-(6-trifluorometoxi-1,3-benzotiazol-2-il)-amina (3,66 g, 9 mmol), 150 ml de tolueno, 60 ml etanol, y 20 ml de $NaHCO_3$ acuoso saturado. Se eliminó el gas de la mezcla burbujeando nitrógeno gaseoso 30 minutos. Se agregó complejo de 1,1'-bis(difenilfosfina)ferroceno)dicloropaladio(II) diclorometano (0,82 g, 1,0 mmol) a la mezcla de reacción. Se calentó la mezcla a 85°C hasta la mañana siguiente. Luego se llevo a cabo el procesamiento en un modo similar al descrito con anterioridad. Se concentró el filtrado a presión reducida y el residuo sólido se sometió a ultrasonido en 100 ml de acetonitrilo durante 30 minutos y se filtró para dar el compuesto deseado como un sólido blanco (2,59 g, 52%). CL-EM *m/z* 559,3 (MH^+), tiempo de ret. 4,75 min.

318.

318

Ácido (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-trifluorometoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico

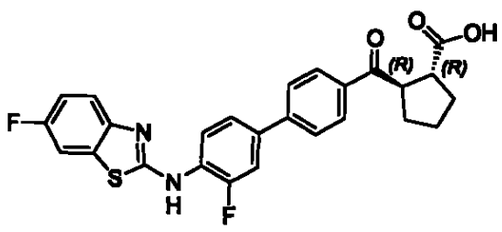


Paso 2. En un balón de 250 ml, se disolvió (1*R*,2*R*)-2-[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxilato de metilo (2,53 g, 4,53 mmol) en 100 ml de THF/dioxano 1:1que contenía 5,0 equivalentes molares de NaOH acuoso 1 N. Se agitó la mezcla a t.a. hasta la mañana siguiente. Se concentró la mezcla a presión reducida hasta un volumen de aproximadamente 20 ml. Se agregaron a la mezcla acetato de etilo (100 ml), agua (30 ml), y 5,1 equivalentes molares de HCl acuoso 1 N. La mezcla se transfirió a un embudo de decantación. Se lavó la fase orgánica con agua (1 x 50 ml), se secó (Na_2SO_4), y se concentró a presión reducida. El sólido se sometió a ultrasonido en 30 ml de acetonitrilo y se filtró para dar el compuesto deseado como un sólido blanco (1,96 g, 80%, 94,5% de ee). ^{1}H RMN (400 MHz, DMSO-d_6) δ 12,20 (br s, 1 H), 10,60 (bs, 1 H), 8,70 (t, 1 H), 7,60-8,20 (m, 8 H), 7,30 (d, 1 H), 4,70 (q, 1 H), 3,20 (q, 1 H), 2,20 (m, 1 H), 2,00 (m, 1 H), 1,50-1,90 (m, 4 H); CL-EM *m/z* 545,3 (MH^+), tiempo de ret. 3,93 min.

Ejemplo 26

Ácido (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico

319

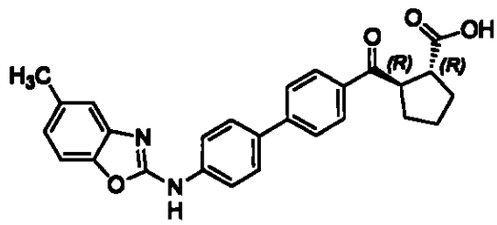


Se preparó (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxilato de *ter*-butilo a partir de (1*R*,2*R*)-2-(4-bromobenzoil)ciclopentancarboxilato de *ter*-butilo y *N*-(4-bromo-2-fluorofenil)-*N*-(6-fluoro-1,3-benzotiazol-2-il)amina de un modo similar al que se describió con anterioridad para el (1*R*,2*R*)-2-[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentancarboxilato de metilo. Se agitó una solución del *ter*-butil éster (1,5 g, 2,81 mmol) en 2,0 ml TFA y 10 ml CH_2Cl_2 a t.a. hasta la mañana siguiente. Luego se eliminó el solvente por evaporación rotativa, se agregaron 50 ml de EtOAc y 50 ml de agua. Se separó la fase orgánica, se lavó con 50 ml de agua, y luego se secó sobre Na_2SO_4. Luego de eliminar el solvente por evaporación rotativa, se agregó al residuo 5 ml de EtOAc, seguido de 5 ml de hexanos. El precipitado que se formó se recolectó por filtración para dar el producto deseado como un sólido amarillo claro (1,0 g, 77%, 95,2% de ee). ^{1}H RMN (400 MHz, DMSO-d_6) δ 12,20 (br s, 1 H), 10,50 (bs, 1 H), 8,70 (t, 1 H), 7,60-8,10 (m, 8 H), 7,20 (t, 1 H), 4,10 (m, 1H), 3,20 (m, 1 H), 2,20 (m, 1 H), 2,00 (m, 1 H), 1,50-1,90 (m, 4 H); CL-EM *m/z* 479,3 (MH^+), tiempo de ret. 3,64 min.

Ejemplo 27

Ácido (1*R*,2*R*)-2-({4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico

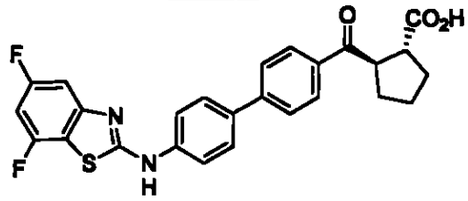
320.



Este compuesto se preparó a partir de *N*-(4-bromofenil)-*N*-(5-metil-1,3-benzoxazol-2-il)amina (0,50 g, 1,65 mmol), (1*R*,2*R*)-2-(4-bromobenzoil) ciclopentan-carboxilato de metilo (0,57 g, 1,83 mmol, 94,5% de ee) de un modo similar al método descrito para el ácido (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-trifluorometoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico. Rendimiento: 17%. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,80 (s, 1 H), 8,05 (d, 2 H), 7,75-7,90 (m, 6 H), 7,35 (d, 1 H), 7,25 (s, 1 H), 6,95 (d, 1 H), 4,05 (q, 1 H), 3,20 (s, 1 H), 2,40 (s, 3 H), 2,15 (m, 1 H), 2,00 (m, 1 H), 1,55-1,80 (m, 4 H). CL-EM *m/z* 441,3 (MH^+), tiempo de ret. 3,48 min.

Ejemplo 28

Ácido *trans*-2-({4'-[(5,7-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico



A una solución de *trans*-2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclobutan-carboxilato de metilo (80 mg, 0,25 mmol) en n-butanol (8 ml) se agregó 2-cloro-5,7-difluoro-1,3-benzotiazol (102 mg, 0,49 mmol) y HCl (4,0 M en dioxano, 0,2 ml). Se calentó la mezcla de reacción resultante a 90°C hasta la mañana siguiente. La mezcla se evaporó hasta sequedad, y el residuo se absorbió en MeOH. Luego se agregó NaOH acuoso 1 N (2,0 ml, 2,0 mmol), y se agitó la mezcla de reacción a 50°C hasta la mañana siguiente. Se concentró la mezcla de reacción y se suspendió el residuo en agua. Se agregó HCl conc. para ajustar la acidez hasta un pH 1, y se extrajo la suspensión con EtOAc. Se lavaron las fases orgánicas

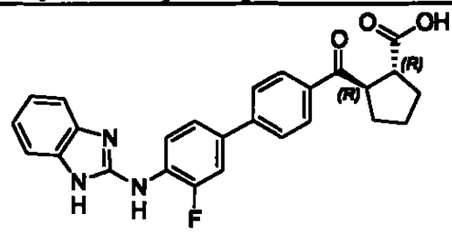
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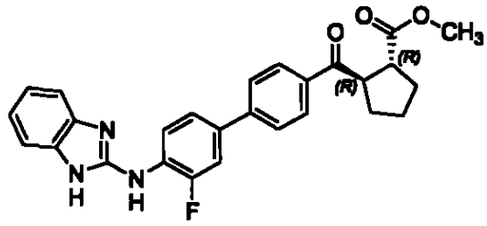
combinadas con salmuera, se secaron sobre sulfato de sodio, se filtraron, y se concentraron. El residuo se absorbió en MeOH, y se recolectó el precipitado por filtración y se secó en estufa de vacío para producir ácido *trans*-2-({4'-[(5,7-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentancarboxílico (65 mg, 58%). Tiempo de retención de CL-EM 3,75; *m/z* 479,2 (MH^+). ^1H RMN (400 MHz, DMSO-d_6) δ 1,55-1,84 (m, 4H), 2,01 (m, 1H), 2,18 (m, 1H), 3,22 (q, 1H), 4,09 (q, 1H), 7,15 (m, 1H), 7,40 (m, 1H), 7,83 (m, 4H), 7,87 (d, 2H), 8,05 (d, 2H), 11,00 (s, 1H), 12,12 (s, 1H).

Ejemplo 29

Ácido (1R,2R)-2-{[4'-(1H-benzoimidazol-2-ilamino)-3'-fluoro-1,1'-bifenil-4-il]carbonil}ciclopentancarboxílico



(1R,2R)-2-{[4'-(1H-benzoimidazol-2-ilamino)-3'-fluoro-1,1'-bifenil-4-il]carbonil}-ciclopentancarboxilato de metilo.

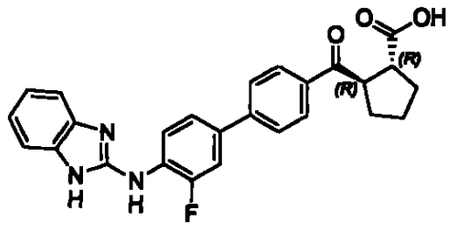


Paso 1. Se combinaron (1*R*,2*R*)-2-[(4'-amino-3'-fluoro-1,1'-bifenil-4-il)carbonil]ciclopentancarboxilato de metilo (100 mg, 0,29 mmol, 80 % de ee) y 2-clorobenzoimiazol (49 mg, 0,32 mmol) en 1,4-dioxano (2 ml) y se trató con un equivalente molar de HCl 4 M en dioxano (73 µl). Se calentó la mezcla a 90°C durante 18 h, luego se enfrió hasta ta y se concentraron a presión reducida a un aceite naranja. Se purificó el residuo por cromatografía flash sobre gel de sílice,

322

eluyendo con 2:1 hexanos/acetato de etilo seguido de metanol para dar el compuesto del título como un aceite oscuro (0,12 g, 90%). ^{1}H RMN (300 MHz, MeOD-d_4) δ 8,09 (d, 2 H), 7,81 (d, 2 H), 7,75-7,67 (m, 3 H), 7,46-7,40 (m, 2 H), 7,32-7,28 (m, 2 H), 4,17-4,09 (m, 1 H), 3,26-3,23 (m, 1 H), 2,24-2,16 (m, 1 H), 2,10-2,02 (m, 1 H), 1,91-1,68 (m, 4 H); CL-EM *m/z* 458,4 (MH^+), tiempo de retención 2,48 minutos; TLC R_f 0,28 (hexanos/acetato de etilo 2:1).

Ácido (1*R*,2*R*)-2-{[4'-(1H-benzoimidazol-2-ilamino)-3'-fluoro-1,1'-bifenil-4-il]carbonil}-ciclopentancarboxílico.

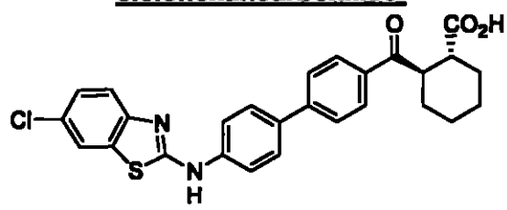


Paso 2. Se disolvió (1*R*,2*R*)-2-{[4'-(1H-bencimidazol-2-ilamino)-3'-fluoro-1,1'-bifenil-4-il]carbonil}ciclopentancarboxilato de metilo (100 mg, 0,22 mmol) en metanol y se trató con un exceso de solución acuosa 1N de hidróxido de sodio (2,19 ml, 2,19 mmol). Se agitó la solución a t.a. durante 1 h, y luego se concentró a presión reducida. Se repartió el residuo entre agua y acetato de etilo, y se ajustó la fase acuosa hasta un pH 2 con el agregado de HCl acuoso 1 N. Se separó la fase orgánica, se lavó con salmuera, se secó ($MgSO_4$), y se concentró a presión reducida para suministrar un aceite naranja. El aceite se suspendió en THF y se agitó hasta que se formó un precipitado. Se recolectó el precipitado por filtración y se lavó con THF adicional para suministrar el compuesto del título como un sólido amarillo (30 mg, 31%, 80% de ee). ^{1}H RMN (300 MHz, DMSO-d_6) δ 13,12 (br s, 1 H), 11,30 (br s, 1 H), 8,12 (d, 2 H), 7,96-7,76 (m, 5 H), 7,46-7,42 (m, 2 H), 7,30-7,26 (m, 2 H), 4,15-4,07 (m, 1 H), 3,27-3,19 (m, 1 H), 2,21-2,12 (m, 1 H), 2,05-1,96 (m, 1 H), 1,86-1,55 (m, 4 H); CL-EM *m/z* 444,4 (MH^+), tiempo de retención 2,79 minutos.

323
323

Ejemplo 30

Ácido *trans*-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil) ciclohexancarboxílico

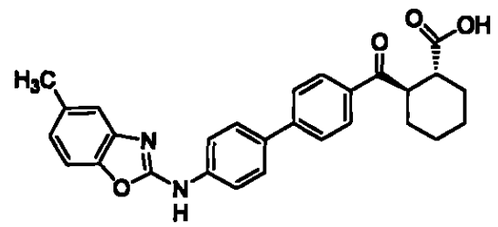


A una solución de 2-[(4'-amino-1,1'-bifenil-4-il)carbonil]ciclohexancarboxilato de *cis*-metilo (200 mg, 0,59 mmol) en n-butanol (8 ml) se agregó 2,6-dicloro-1,3-benzotiazol (241 mg, 1,19 mmol), y se calentó la mezcla de reacción resultante a 90°C hasta la mañana siguiente. La mezcla se evaporó hasta la sequedad y se combinó el residuo con MeOH. Luego se agregó a la suspensión NaOH 1 N (6,0 ml, 6,0 mmol), y se agitó la mezcla de reacción a 50°C hasta la mañana siguiente. Se concentró la mezcla de reacción a presión reducida, y se suspendió el residuo en agua. Se agregó HCl concentrado acuoso para ajustar la acidez hasta un pH 1, y se recolectó el precipitado por filtración, se lavó con agua y MeOH, y se secó en estufa de vacío para dar ácido *trans*-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclohexancarboxílico (45 mg, 15%). CL-EM *m/z* 491,1 (MH^+), tiempo de ret. 3,90 min; ^1H RMN (400 MHz, DMSO-d_6) δ 1,13 (m, 1H), 1,28 ~ 1,51 (m, 3H), 1,78 (m, 1H), 1,93 (m, 1H), 2,09 (m, 1H), 2,68 (m, 1H), 3,63 (m, 1H), 7,35 (m, 1H), 7,60 (m, 1H), 7,80 (m, 4H), 7,90 (d, 1H), 7,96 (m, 1H), 8,05 (d, 2H), 10,75 (s, 1H).

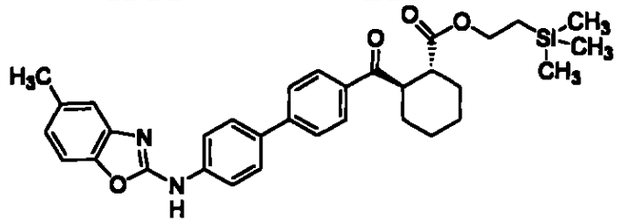
Ejemplo 31

Ácido *trans*-2-({4'-[(5-metil-1,3-benzoxazol-2-il)amino]bifenil-4-il}carbonil) ciclohexancarboxílico

324



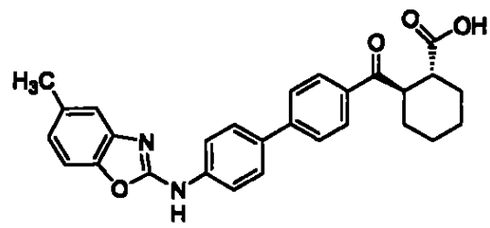
trans-2-(Trimetilsilil)etil-2-({4'-[(5-metil-1,3-benzoxazol-2-il)amino]-bifenil-4-il}carbonil)ciclohexancarboxilato



Paso 1. Se combinaron *N*-(4-bromofenil)-5-metil-1,3-benzoxazol-2-amina (76,70 mg, 0,25 mmol) y *trans*-2-(trimetilsilil)etil-2-(4-bromobenzoil)ciclohexan-carboxilato (105,45 mg, 0,23 mmol) en un matraz limpio bajo argón. Se agregaron tolueno (25 ml), EtOH (8 ml), y $NaHCO_3$ acuoso saturado (5 ml), y la solución resultante se desgasificó burbujeando con argón durante 30 minutos. Luego, se agregó [1,1'-bis(difenilfosfina)-ferroceno]dicloro paladio(II), complejo 1:1 con diclorometano (18,78 mg, 0,02 mmol), y se calentó la mezcla resultante a 90°C durante 16 h. Luego se diluyó la mezcla de reacción con EtOAc y se pasó a través de un taco de Celite®, y se eliminó el solvente por evaporación rotativa. La cromatografía sobre gel de sílice (cartucho Biotage), eluyendo con 25% EtOAc en hexano dio *trans*-2-(trimetilsilil)etil-2-({4'-[(5-metil-1,3-benzoxazol-2-il)amino]bifenil-4-il}carbonil)ciclohexancarboxilato (64 mg, 50%). ^1H RMN (400 MHz, CD_2Cl_2) δ –0,013 (s, 9H), 0,88 (m, 2H), 1,41 (m, 3H), 1,71 – 2,15 (m, 5H), 2,44 (s, 3H), 2,73 (m, 1H), 3,88 (m, 1H), 4,08 (m, 2H), 7,08 (d, 1H), 7,21 (s, 1H), 7,33 (d, 1H), 7,67 (m, 2H), 7,69 (m, 2H), 7,73 (m, 2H), 7,89 (m, 1H), 7,91 (m, 1H).

Ácido *trans*-2-({4'-[(5-Metil-1,3-benzoxazol-2-il)amino]bifenil-4-il}-carbonil)ciclohexancarboxílico.

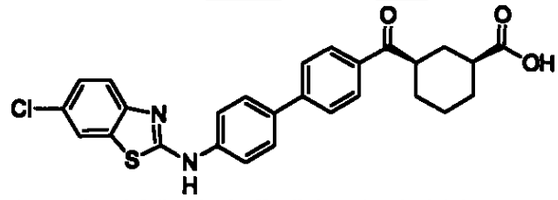
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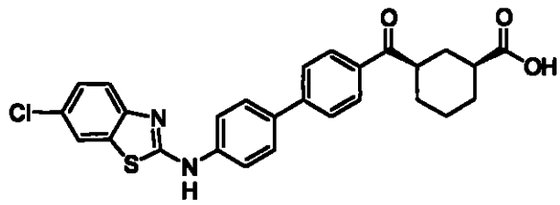
Paso 2. A una solución de *trans*-2-(trimetilsilil)etil-2-({4'-[(5-metil-1,3-benzoxazol-2-il)amino]bifenil-4-il}carbonil)ciclohexancarboxilato (64 mg, 0,12mmol) en THF (2 ml) se agregó fluoruro de tetrabutilamonio (1,0 M en THF, 0,70 ml), y luego se agitó la mezcla de reacción a t.a. durante 16 h. se agregó, NH_4Cl acuoso saturado y se diluyó la mezcla de reacción con EtOAc y agua. Se separó la fase orgánica y se extrajo la fase acuosa con EtOAc. Se lavaron las fases orgánicas combinadas con agua y salmuera, se secaron sobre Na_2SO_4, se filtraron, y se evaporaron a presión reducida. El residuo se trató con MeOH, y se recolectó el precipitado por filtración y se secó en estufa de vacío para dar ácido *trans*-2-({4'-[(5-metil-1,3-benzoxazol-2-il)amino]bifenil-4-il}carbonil)ciclohexancarboxílico (44,3 mg, 84%). CL-EM *m/z* 455,3 (MH^+), tiempo de ret. 3,57 min. ^1H RMN (400 MHz, DMSO-d_6) δ 1,21 (m, 1H), 1,37 (m, 2H), 1,63 (m, 1H), 1,85 (m, 3H), 2,05 (m, 1H), 2,38 (s, 3H), 2,69 (m, 1H), 3,95 (m, 1H), 7,03 (d, 1H), 7,33 (d, 2H), 7,76 (m, 4H), 7,85 (d, 2H), 7,93 (d, 2H), 10,73 (s, 1H).

Ejemplo 32

Ácido *cis*-3-[4'-(6-cloro-benzotiazol-2-ilamino)-bifenil-4-carbonil]-ciclohexancarboxílico



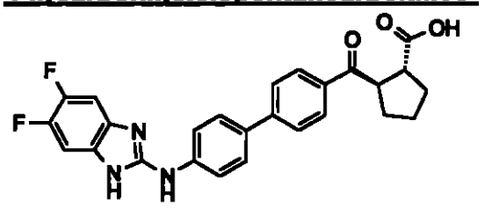
Ácido *cis*-3-[4'-(6-cloro-benzotiazol-2-ilamino)-bifenil-4-carbonil]ciclohexan-carboxílico



A una solución del metil éster del ácido 3-(4'-amino-bifenil-4-carbonil)-ciclohexancarboxílico (100 mg, 0,3 mmol) en butanol (5 ml), 2,6-dicloro-benzotiazol (60 mg, 0,3 mmol) y se agregaron 5 gotas de HCl 4 M en dioxano, y se calentó la mezcla de reacción a 90°C durante 5 h. Una muestra adicional de 2,6-diclorobenzotiazol (60 mg, 0,3 mmol) y luego se agregaron 5 gotas de HCl 4 M en dioxano, y la mezcla de reacción se calentó hasta la mañana siguiente a 90°C. Se eliminó el solvente por evaporación rotativa, se disolvió el residuo en DMF (2 ml), NaOH acuoso 1 N (0,3 ml, 0,3 mmol) se agregó, y se calentó la mezcla a 75°C hasta la mañana siguiente. Una solución de HCl acuoso 1 N (0,3 ml, 0,3 mmol) y metanol (5 ml) se agregaron a la mezcla de reacción, y se purificó el producto en bruto por HPLC preparativa de fase inversa (gradiente agua/acetonitrilo, que contenía 0,1% de TFA) para producir ácido *cis*-3-[4'-(6-cloro-benzotiazol-2-ilamino)-bifenil-4-carbonil]-ciclohexancarboxílico como un sólido blanco (12,6 mg, rendimiento 23,4%). ^{1}H RMN (300 MHz, DMSO) δ 8,05 (d, 2 H), 7,75-8,00 (m, 7 H), 7,50 (d, 1 H), 7,35 (d, 1 H), 3,25 (m, 1 H), 2,50 (m, 1 H), 2,20-1,90 (m, 4 H), 1,70-1,50 (m, 4 H); Tiempo de retención de CL-EM 3,99 min (método 2), *m/z* 491,11 (MH^+).

Ejemplo 33

Ácido *trans*-2-{(4'-[(5,6-difluoro-1H-bencimidazol-2-il)amino]bifenil-4-il}carbonil)ciclopentancarboxílico



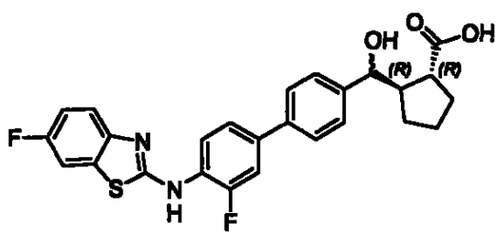
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Se disolvió 2-[(4'-aminobifenil-4-il)carbonil]ciclopentancarboxilato de metilo (264 mg, 0,02 mmol) en n-butanol (8 ml), luego se agregaron 2-cloro-5,6-difluoro-1H-bencimidazol (185 mg, 0,98 mmol) y HCl 4 N (0,2 ml), y se calentó la mezcla resultante a 90°C durante 5 h. Luego se enfrió la mezcla hasta ta, y se eliminó el solvente a presión reducida. Se disolvió el residuo en metanol (5 ml) y tetrahidrofurano (5 ml), y luego se trató con hidróxido de sodio acuoso 1 N (2,45 ml, 2,45 mmol). Se agitó la mezcla a t.a. durante 16 h y luego se concentró a presión reducida. Se purificó el residuo por HPLC preparativa de fase inversa (Gradiente agua/ acetonitrilo, que contenía 0,1% de TFA) para producir ácido *trans*-2-({4'-[(5,6-difluoro-1H-benzoimidazol-2-il)amino]bifenil-4-il}carbonil)-ciclopentancarboxílico (9,1 mg, 3 %). CL-EM *m/z* 462,3 (MH^+), tiempo de ret. 3,23 min; ^1H RMN (300 MHz, DMSO-d_6) δ 1,69- 1,81 (m, 4H), 1,98-2,18 (m, 2H), 3,14-3,22 (m, 1H), 4,04-4,09 (m, 1H), 7,38 (t, 2H), 7,77-7,84 (m, 6H), 8,05 (d, 2H).

Preparación de los Compuestos de Fórmula (Ia)

Ejemplo 34

Ácido (1*R*,2*R*)-2-[{3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}(hidroxi)metil]ciclopentancarboxílico



A una solución de ácido (1*R*,2*R*)-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}carbonil)ciclopentancarboxílico (300 mg, 0,63 mmol) en THF (6 ml), se agregó una solución de borohidruro de sodio (23,82 mg, 0,63 mmol) en

328
328

agua (3 ml). Se agitó la mezcla de reacción a t.a. durante 3 horas. Se eliminó el solvente, el residuo se disolvió luego en metanol (2 ml), y el producto deseado se aisló por HPLC preparativa de fase inversa (gradiente agua/acetonitrilo, que contenía 0,1% de TFA). Se obtuvieron dos diastereómeros de ácido (1*R*,2*R*)-2-[{3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}(hidroxi)metil]-ciclopentancarboxílico: un isómero más polar (15 mg, rendimiento 5%). CL-EM *m/z* 481,3 (MH^+), tiempo de ret. 3,33 min; ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,60 (t, 1 H), 7,60 (d, 1 H), 7,50 (m, 5 H), 7,35 (d, 2 H), 7,15 (t, 1 H), 4,60 (d, 1 H), 2,65 (m, 1 H), 2,45 (m, 1 H), 1,85 (m, 1 H), 1,70-1,40 (m, 5 H); y un isómero menos polar (10 mg, rendimiento 3%); CL-EM *m/z* 481,3 (MH^+), tiempo de ret. 3,46 min; ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,60 (t, 1 H), 7,60 (d, 1 H), 7,50 (m, 5 H), 7,35 (d, 2 H), 7,15 (t, 1 H), 4,60 (d, 1 H), 2,65 (m, 1 H), 2,45 (m, 1 H), 1,85 (m, 1 H), 1,65 (m, 1 H), 1,50 (m, 3 H), 1,25 (m, 1 H).

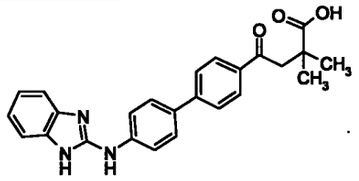
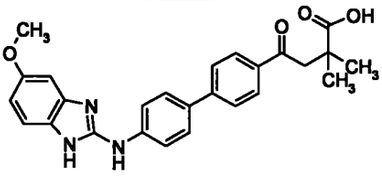
Preparación de los Compuestos de Fórmula (Ib)

Aquellos expertos en el arte reconocerán que los compuestos de Fórmula (Ia) pueden convertirse en y aislarse como el correspondiente éster cíclico (lactona) que tienen la Fórmula (Ib), por ejemplo por deshidratación espontánea del compuesto de Fórmula (Ia), o por deshidratación del compuesto de Fórmula (Ib) inducida por métodos conocidos en el arte. Por ejemplo, dichos métodos para la formación de compuestos de Fórmula (Ib) a partir de compuestos de Fórmula (Ia) incluyen calentamiento en condiciones anhidras tales como en estufa de vacío; tratamiento con una cantidad catalítica de ácido tales como ácido acético, ácido 4-toluensulfónico, o ácido trifluoroacético en un solvente apropiado tal como acetonitrilo, cloruro de metileno, o tolueno; y tratamiento con un agente de deshidratación tal como diciclohexilcarbodiimida en presencia de 4-dimetilaminopiridina en un solvente apropiado tal como acetonitrilo, cloruro de metileno, o tolueno.

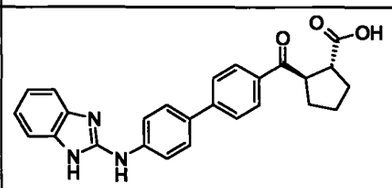
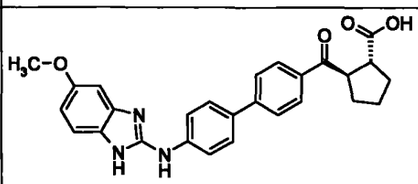
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Usando los materiales de partida apropiados y los experimentos experimentales descritos anteriormente, se prepararon los compuestos de Fórmula (I) como se indica en la Tabla 1. Pueden prepararse compuestos adicionales de Fórmula (Ia) mediante el uso de materiales de partida apropiados y procedimientos similares al que se describió con anterioridad para el ácido (1*R*,2*R*)-2-[{3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]bifenil-4-il}(hidroxi)metil]ciclopentancarboxílico. Los compuestos de Fórmula (Ib) pueden prepararse mediante el uso de compuestos apropiados de Fórmula (Ia) como materiales de partida y la aplicación de métodos tales como los descritos con anterioridad. Los compuestos adicionales de Fórmula (I), Fórmula (Ia), y Fórmula (Ib) tales como los compuestos mencionados en la Tabla 2, pueden prepararse a través de los métodos descritos aquí. Aquellos expertos en el arte comprenderán que pueden haberse realizado modificaciones a los procedimientos descritos, pero dichas modificaciones no afectan significativamente los resultados de la preparación. La caracterización de los compuestos por CL-EM, como se indica en la Tabla, se llevó a cabo mediante el uso de la instrumentación y los métodos establecidos con anterioridad.

Mediante el uso de los métodos descritos anteriormente y sustituyendo el(los) material(es) de partida apropiados, se realizaron y caracterizaron otros compuestos de la invención. Estos compuestos, junto con los Ejemplos 1-34, se resumen en la Tabla 1 a continuación.

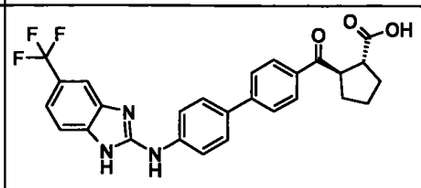
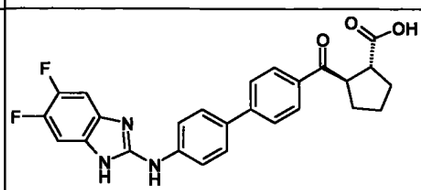
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
1		ácido 4-[4'-(1H-bencimidazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoico	414,3	2,27	1	B	no quiral		2
2		ácido 4-{4'-[(5-metoxi-1H-bencimidazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico	444,4	2,37	1	B	no quiral		

331

No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
3		ácido 2-{[4'-(1H-bencimidazol-2-ilamino)-1,1'-bifenil-4-il]carbonil}ciclopentan-carboxílico	426,4	2,82	1	B	mezcla trans racémica		
4		ácido 2-({4'-[(5-metoxi-1H-bencimidazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	456,3	2,31	1	B	mezcla trans racémica		

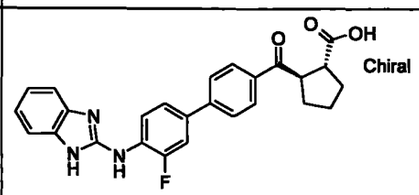
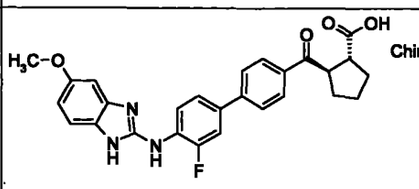
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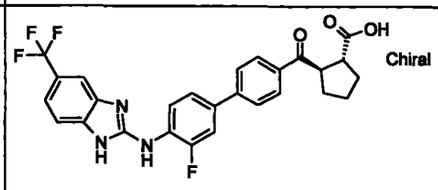
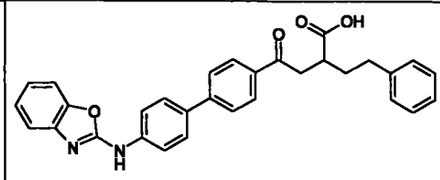
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
5		ácido 2-[(4'-{[5-(trifluorometil)-1H-bencimidazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico	494,3	2,56	1	A	mezcla trans racémica		
6		ácido 2-({4'-[(5,6-difluoro-1H-bencimidazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	462,3	3,23	1	B	mezcla trans racémica		33

332

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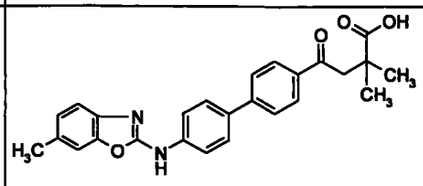
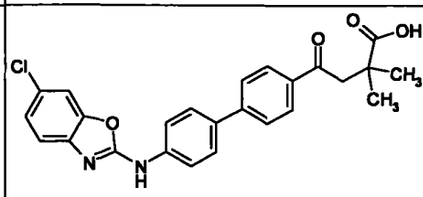
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
7		ácido (1R,2R)-2-{[4'-(1H-bencimidazol-2-ilamino)-3'-fluoro-1,1'-bifenil-4-il]carbonil}ciclopentan-carboxílico	444,4	2,80	1	B	R,R-trans (de intermediario quiral)	80	29
8		Ácido (1R,2R)-2-({3'-fluoro-4'-[(5-metoxi-1H-bencimidazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	474,3	2,29	1	B	R,R-trans (de intermediario quiral)	74	

334

No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
9	 Chiral	ácido (1R,2R)-2-[(3'-fluoro-4'-{[5-(trifluorometil)-1H-bencimidazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico	512,3	2,69	1	A	R,R-trans (de intermediario quiral)	78	
10		ácido 4-[4'-(1,3-benzoxazol-2-ilamino)-1,1'-bifenil-4-il]-4-oxo-2-(2-feniletil)butanoico	491,2	3,68	1	B	mezcla racémica		11

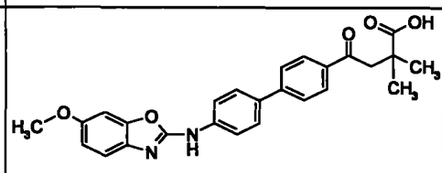
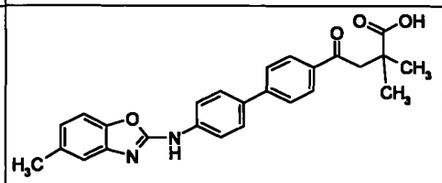
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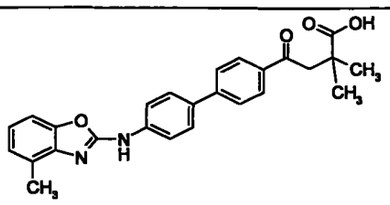
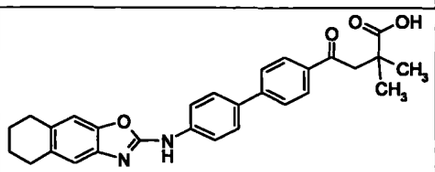
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
11		ácido 2,2-dimetil-4-{4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico	429,2	3,51	2	B	no quiral		12
12		ácido 4-{4'-[(6-cloro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico	449,1	3,99	2	B	no quiral		

335

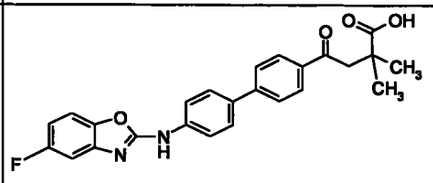
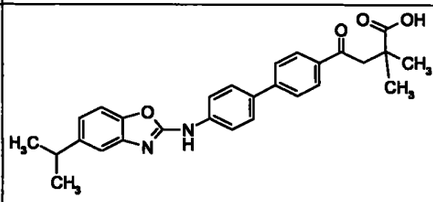
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
13		ácido 4-{4'-[(6-metoxi-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico	445,2	3,47	2	B	no quiral		
14		ácido 2,2-dimetil-4-{4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico	429,2	3,77	2	B	no quiral		

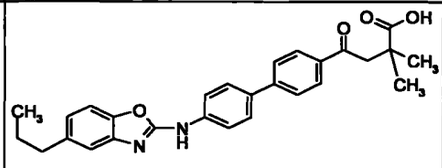
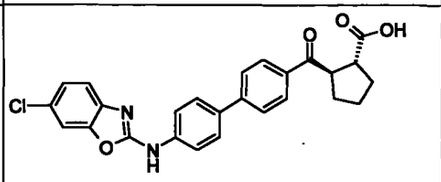
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
15		ácido 2,2-dimetil-4-(4'-[(4-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il)-4-oxobutanoico	433,2	3,80	2	B	no quiral		13
16		ácido 2,2-dimetil-4-oxo-4-[4'-(5,6,7,8-tetrahidronafto[2,3-d][1,3]oxazol-2-ilamino)-1,1'-bifenil-4-il]butanoico	469,2	3,99	2	B	no quiral -		

338

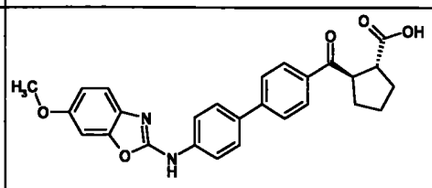
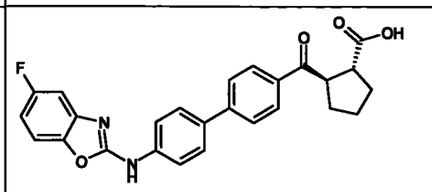
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
17		ácido 4-{4'-[(5-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico	433,2	3,80	2	B	no quiral		
18		ácido 4-{4'-[(5-isopropil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico	457,2	3,88	2	B	no quiral		

339

No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
19		ácido 2,2-dimetil-4-oxo-4-{4'-[(5-propil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}butanoico	457,2	3,95	2	B	no quiral		
20		ácido 2-({4'-[(6-cloro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	461,1	3,84	2	B	mezcla trans racémica		

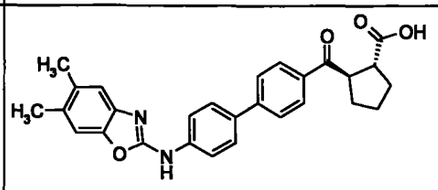
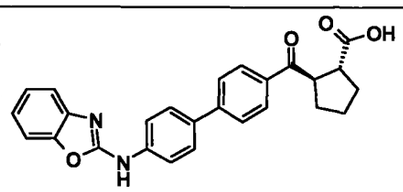
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
21		ácido 2-({4'-[(6-metoxi-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	457,2	3,55	2	B	mezcla trans racémica		
22		ácido 2-({4'-[(5-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	445,2	3,66	2	B	mezcla trans racémica		14

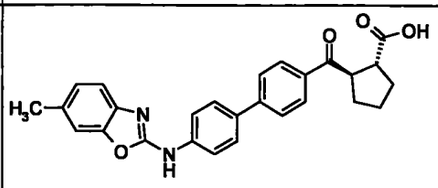
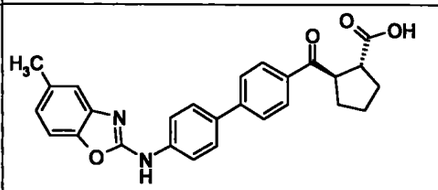
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
23		ácido 2-({4'-[(5,6-dimetil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	455,4	3,58	1	B	mezcla trans racémica		
24		ácido 2-({4'-(1,3-benzoxazol-2-ilamino)-1,1'-bifenil-4-il]carbonil}ciclopentan-carboxílico	427,3	3,31	1	B	mezcla trans racémica		

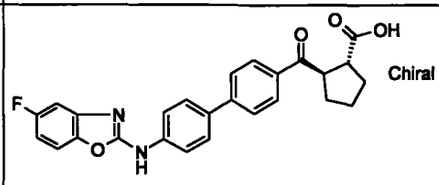
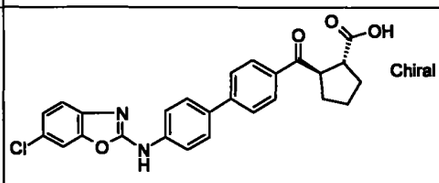
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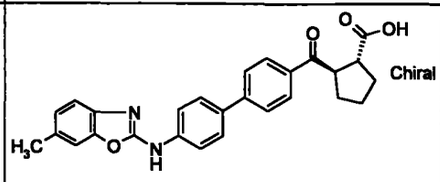
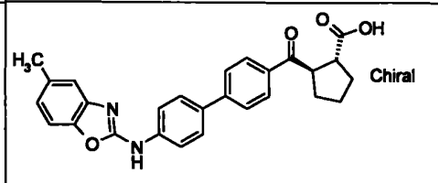
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
25		ácido 2-({4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	441,2	3,88	2	B	mezcla trans racémica		
26		ácido 2-({4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	441,2	3,84	2	B	mezcla trans racémica		

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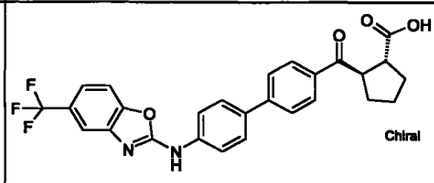
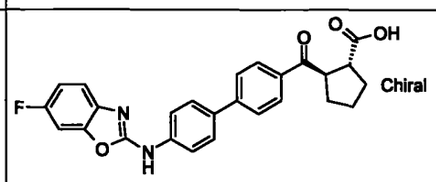
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
27		ácido (1R,2R)-2-{(4'-[(5-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	445,3	3,41	1	B	R,R-trans (de intermediario quiral)	94	
28		ácido (1R,2R)-2-{(4'-[(6-cloro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	461,4	3,67	1	B	R,R-trans (de intermediario quiral)	97	

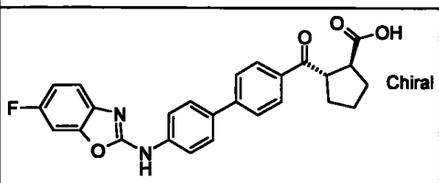
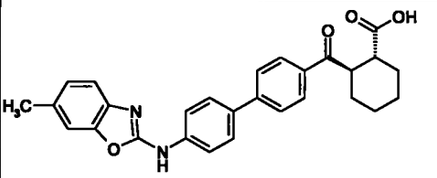
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
29		ácido (1R,2R)-2-({4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	441,3	3,47	1	B	R,R-trans (de intermediario quiral)	80	
30		ácido (1R,2R)-2-{{4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	441,3	3,48	1	A	R,R-trans (de HPLC prep. quiral)	96	27

345

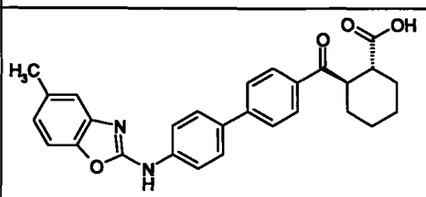
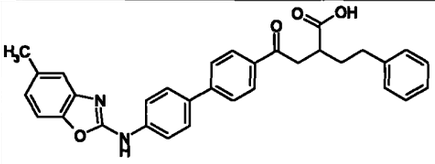
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
31	 Chiral	ácido (1R,2R)-2-[(4'-{[5-(trifluorometil)-1,3-benzoxazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico	495,3	4,15	1	A	R,R-trans (de intermediario quiral)	98	
32	 Chiral	ácido (1R,2R)-2-({4'-[(6-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	445,2	3,39	1	B	R,R-trans (de HPLC prep. quiral)	>99	

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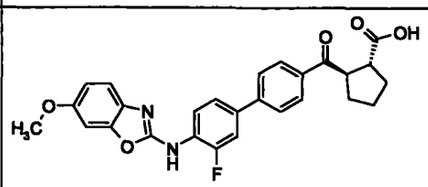
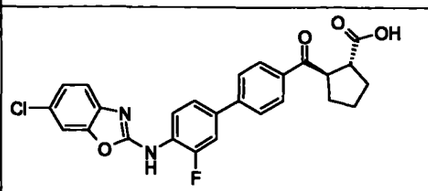
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
33		ácido (1S,2S)-2-({4'-[(6-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	445,2	3,39	1	B	S,S-trans (de HPLC prep. quiral)	>99	
34		ácido 2-({4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclohexan-carboxílico	455,3	3,57	1	A	mezcla trans racémica		

345

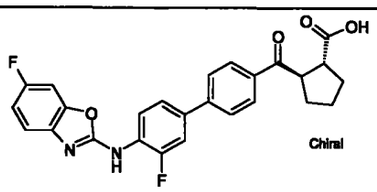
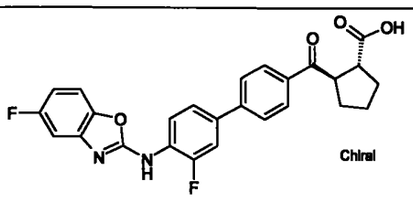
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
35		ácido 2-({4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclohexan-carboxílico	455,3	3,57	1	A	mezcla trans racémica		31
36		ácido 4-{4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxo-2-(2-feniletil)butanoico	505,3	3,74	1	A	mezcla racémica		

348

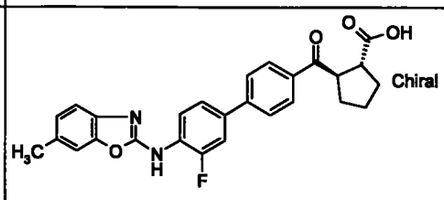
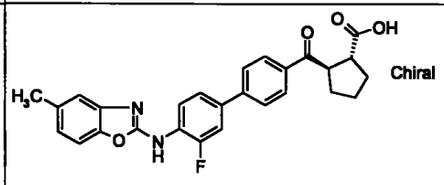
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
37		ácido 2-({3'-fluoro-4'-[(6-metoxi-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	475,2	3,29	2	B	mezcla trans racémica		
38		ácido 2-({4'-[(6-cloro-1,3-benzoxazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	479,1	3,77	2	B	mezcla trans racémica		

349

No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
39		ácido (1R,2R)-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	463,3	3,44	1	B	R,R-trans (de HPLC prep. quiral)	80	
40		ácido (1R,2R)-2-({3'-fluoro-4'-[(5-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	463,3	3,42	1	B	R,R-trans (de HPLC prep. quiral)	82	

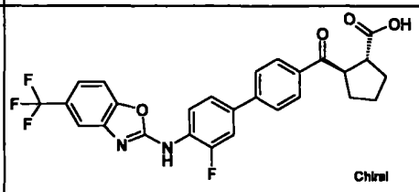
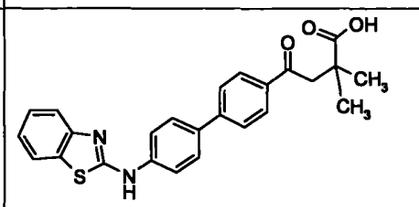
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
41		ácido (1R,2R)-2-({3'-fluoro-4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	459,3	3,57	1	B	R,R-trans (de intermediario quiral)	80	15
42		ácido (1R,2R)-2-({3'-fluoro-4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	459,3	3,54	1	A	R,R-trans (de intermediario quiral)	94	

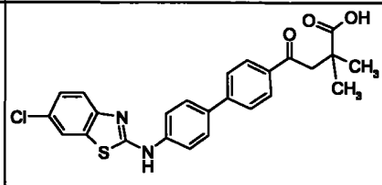
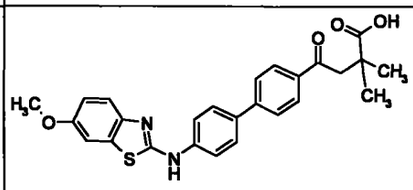
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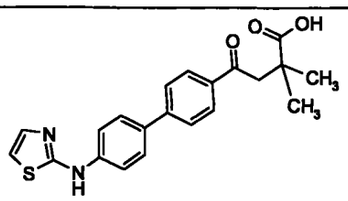
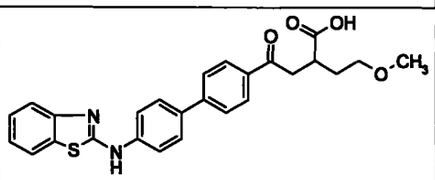
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
43	 Chiral	ácido (1R,2R)-2-[(3'-fluoro-4'-{[5-(trifluorometil)-1,3-benzoxazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico	513,3	4,53	1	A	R,R-trans (de intermediario quiral)	96	
44		ácido 4-[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoico	431,2	3,40	1	B	no quiral		1

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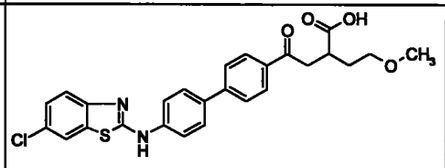
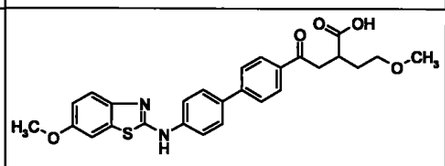
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
45		ácido 4-{4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico	465,2	3,76	1	B	no quiral		
46		ácido 4-{4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico	461,2	3,40	1	B	no quiral		

353

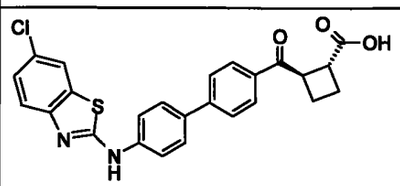
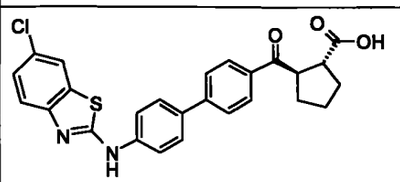
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
47		ácido 2,2-dimetil-4-oxo-4-[4'-(1,3-tiazol-2-ilamino)-1,1'-bifenil-4-il]butanoico	381,4	2,53	1	B	no quiral		3
48		ácido 4-[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2-(2-metoxietil)-4-oxobutanoico	461,2	3,29	2	B	mezcla racémica		6

354

No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
49		ácido 4-{4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2-(2-metoxietil)-4-oxobutanoico	495,1	3,66	2	B	mezcla racémica		
50		ácido 4-{4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2-(2-metoxietil)-4-oxobutanoico	491,2	3,25	2	B	mezcla racémica		

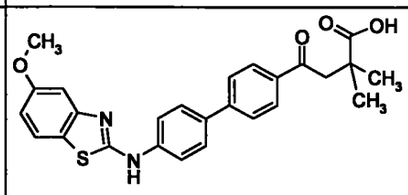
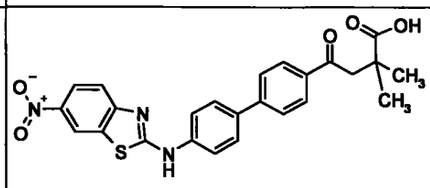
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
51		ácido 2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclobutan-carboxílico	463,1	3,69	1	B	mezcla trans racémica		19
52		ácido 2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	477,4	3,81	1	B	mezcla trans racémica		

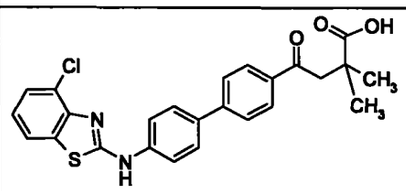
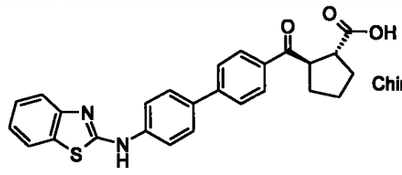
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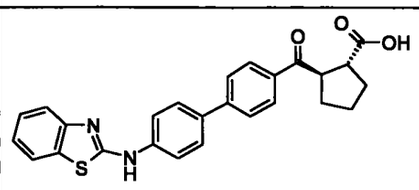
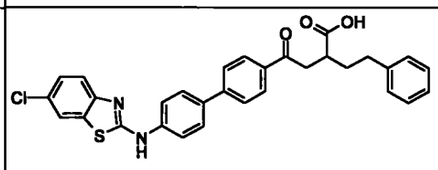
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53		ácido 4-{4'-[(5-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico	461,4	3,33	1	B	no quiral		
54		ácido 2,2-dimetil-4-{4'-[(6-nitro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico	476,2	3,49	1	B	no quiral		

356

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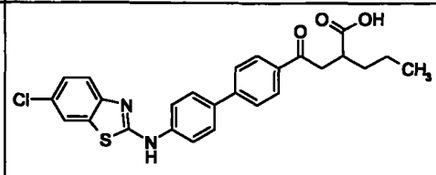
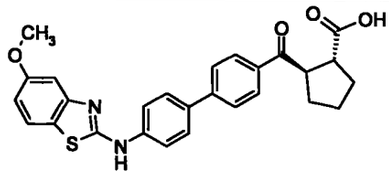
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55		ácido 4-{4'-[(4-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico	465,4	3,62	1	B	no quiral		
56		ácido (1R,2R)-2-{[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]carbonil}ciclopentan-carboxílico	443,3	3,43	1	B	R,R-trans (de intermediario quiral)	97	

358

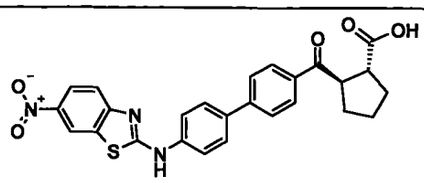
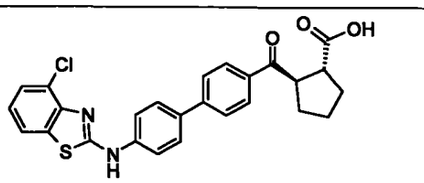
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57		ácido 2-{[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]carbonil}ciclopentan-carboxílico	443,4	3,48	1	B	mezcla trans racémica		
58		ácido 4-{4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxo-2-(2-feniletil)butanoico	541,3	4,07	1	B	mezcla racémica		4

358

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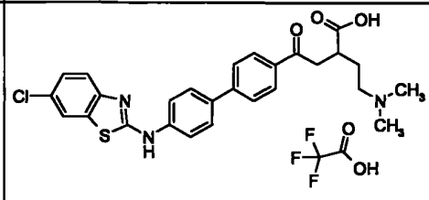
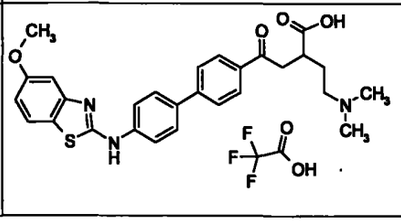
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59		ácido 2-(2-{4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2-oxoetil) pentanoico	479,3	3,88	1	B	mezcla racémica		5
60		ácido 2-({4'-[(5-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	473,3	3,42	1	B	mezcla trans racémica		

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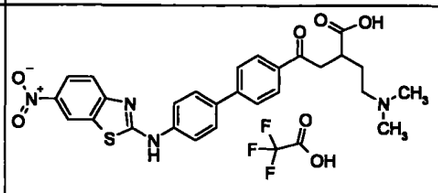
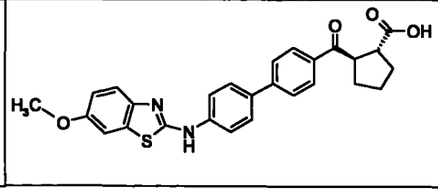
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
61		ácido 2-({4'-[(6-nitro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	488,2	3,59	1	B	mezcla trans racémica		
62		ácido 2-({4'-[(4-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	477,3	3,72	1	B	mezcla trans racémica		

360

361

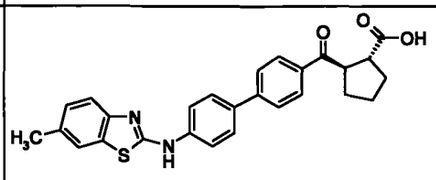
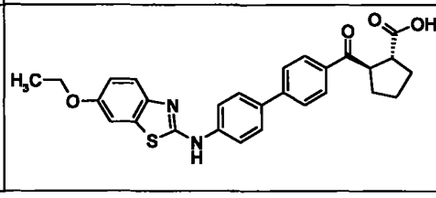
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
63		ácido 4-{4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2-[2-(dimetilamino)etil]-4-oxobutanoico (sal de trifluoroacetato)	508,1	2,66	1	B	mezcla racémica		7
64		ácido 2-[2-(dimetilamino)etil]-4-{4'-[(5-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico (sal de trifluoroacetato)	504,2	2,42	1	B	mezcla racémica		

362

No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
65		ácido 2-[2-(dimetilamino)etil]-4-{4'-[(6-nitro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico (sal de trifluoroacetato)	519,2	2,52	1	B	mezcla racémica		
66		ácido 2-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	473,3	3,41	1	B	mezcla trans racémica		

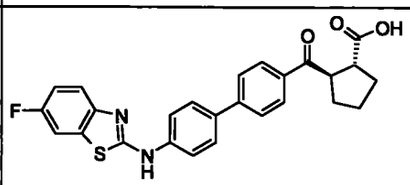
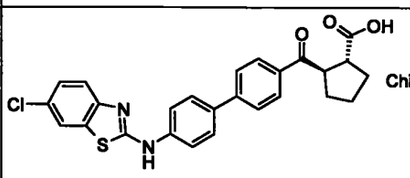
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM *m/z* (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
67		ácido 2-({4'-[(6-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	457,3	3,57	1	A	mezcla trans racémica		20
68		ácido 2-({4'-[(6-etoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	487,4	3,64	1	B	mezcla trans racémica		

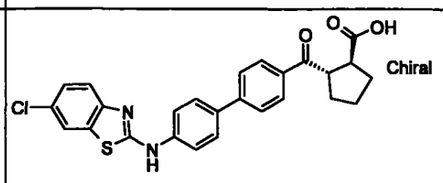
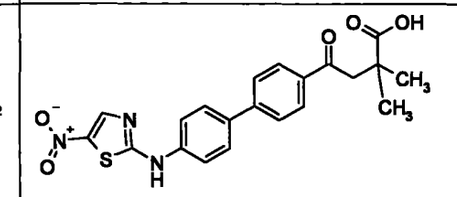
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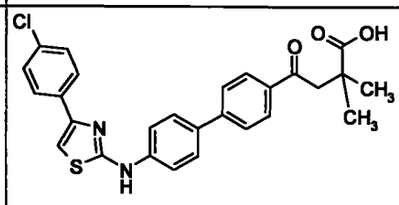
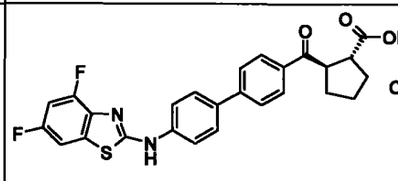
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
69		ácido 2-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	461,4	3,63	1	B	mezcla trans racémica		
70		ácido (1R,2R)-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	477,4	3,85	1	B	R,R-trans (de HPLC prep. quiral)	99	

364

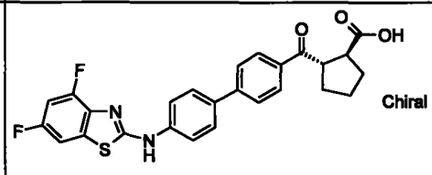
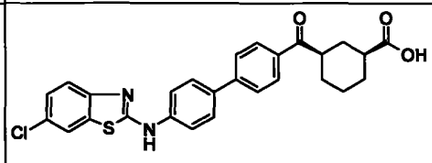
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
71		ácido (1S,2S)-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	477,4	3,85	1	B	S,S-trans (de HPLC prep. quiral)	92	
72		ácido 2,2-dimetil-4-{4'-[(5-nitro-1,3-tiazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico	426,2	3,14	1	B	no quiral		9

366

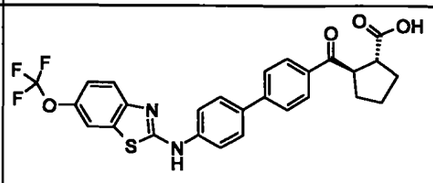
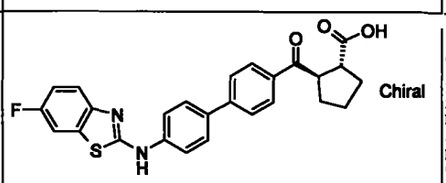
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
73		ácido 4-(4'-{[4-(4-clorofenil)-1,3-tiazol-2-il]amino}-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoico	491,2	3,83	1	B	no quiral		10
74		ácido (1R,2R)-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	479,2	3,64	1	B	R,R-trans (de HPLC prep. quiral)	99	23

367

No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
75		ácido (1S,2S)-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	479,2	3,65	1	B	S,S-trans (de HPLC prep. quiral)	74	24
76		ácido 3-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclohexan-carboxílico	491,1	3,99	2	B	mezcla cis racémica		32

367

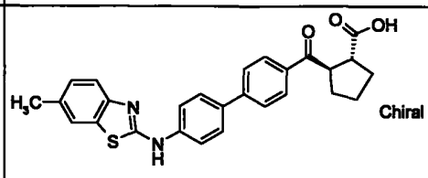
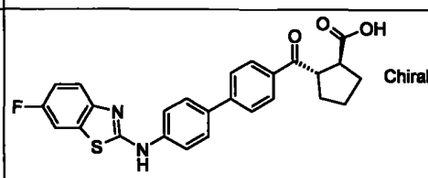
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
78		ácido 2-[(4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico	527,3	3,87	1	B	mezcla trans racémica		
79		ácido (1R,2R)-2-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il)carbonil)ciclopentan-carboxílico	461,1	3,63	1	B	R,R-trans (de HPLC prep. quiral)	99	

Chiral

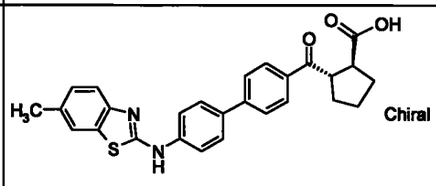
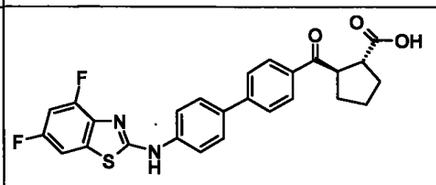
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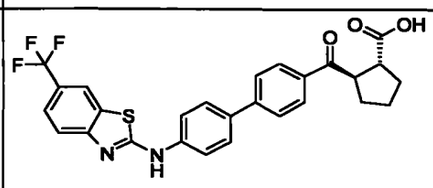
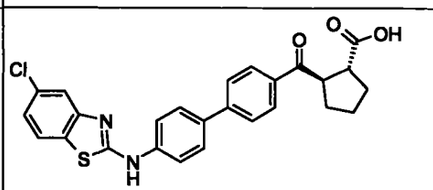
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
80	 Chiral	ácido (1R,2R)-2-[{4'-[(6-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	457,4	3,57	1	B	R,R-trans (de HPLC prep. quiral)	99	
81	 Chiral	ácido (1S,2S)-2-[{4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	461,3	3,55	1	B	S,S-trans (de HPLC prep. quiral)	99	

369

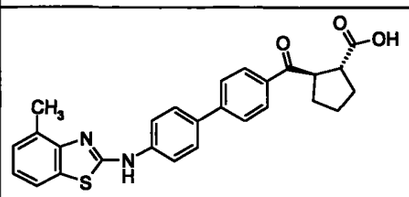
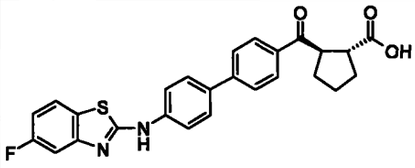
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
82	 Chiral	ácido (1S,2S)-2-({4'-[(6-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	457,4	3,57	1	B	S,S-trans (de HPLC prep. quiral)	99	
83		ácido 2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	479,3	4,12	1	B	mezcla trans racémica		22

371

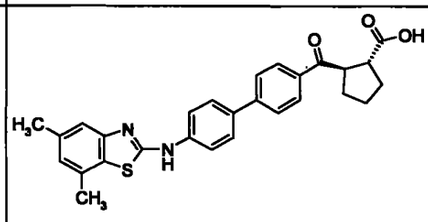
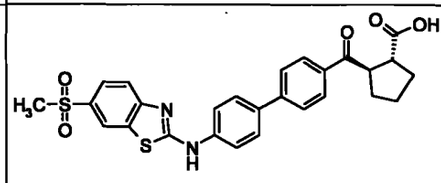
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
86		ácido 2-[{4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il]carbonil]ciclopentan-carboxílico	511,3	4,27	1	B	mezcla trans racémica		17
87		ácido 2-({4'-[(5-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	477,2	3,78	1	B	mezcla trans racémica		

312

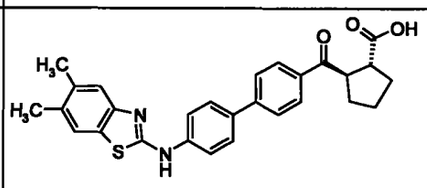
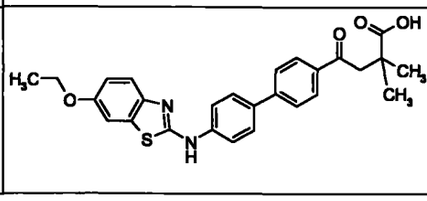
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
84		ácido 2-({4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	457,3	3,71	1	B	mezcla trans racémica		
85		ácido 2-({4'-[(5-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	461,3	3,56	1	B	mezcla trans racémica		16

342

373

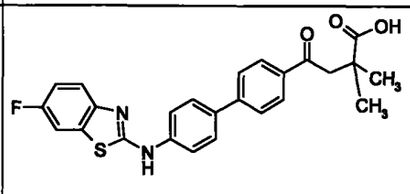
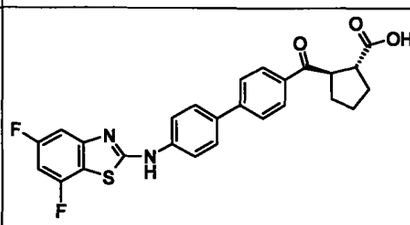
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88		ácido 2-({4'-[(5,7-dimetil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	471,3	3,70	1	B	mezcla trans racémica		
89		ácido 2-[(4'-{[6-(metilsulfonil]-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico	521,2	3,60	1	B	mezcla trans racémica		

374

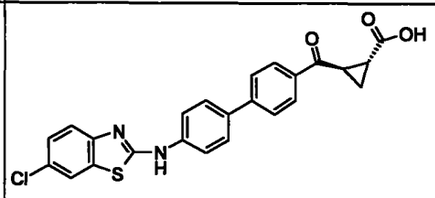
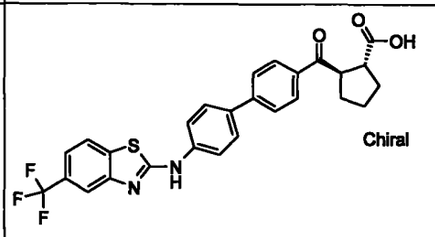
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90		ácido 2-({4'-[(5,6-dimetil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	471,3	3,65	1	B	mezcla trans racámica		
91		ácido 4-{4'-[(6-etoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico	475,2	3,47	1	B	no quiral		

314

375

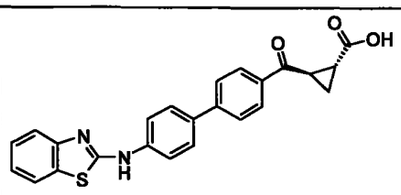
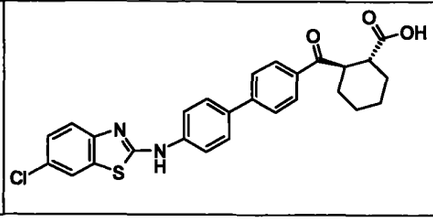
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92		ácido 4-{4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico	449,2	3,46	1	B	no quiral		
93		ácido 2-({4'-[(5,7-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	479,2	3,75	1	B	mezcla trans racémica		28

376

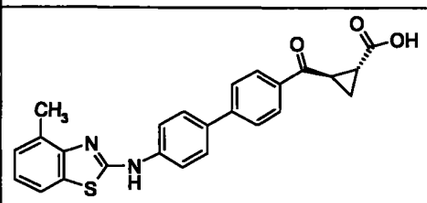
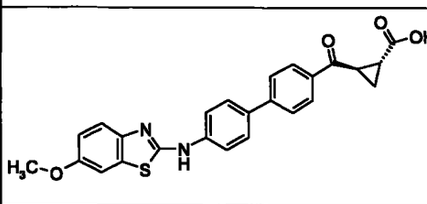
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
94		ácido 2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopropan-carboxílico	449,2	3,70	1	B	mezcla trans racémica		
95		ácido (1R,2R)-2-[(4'-{[5-(trifluorometil)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico	511,1	3,82	1	A	R,R-trans (de intermediario quiral)	90	

376

377

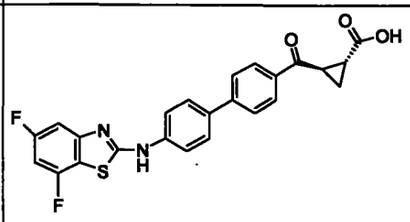
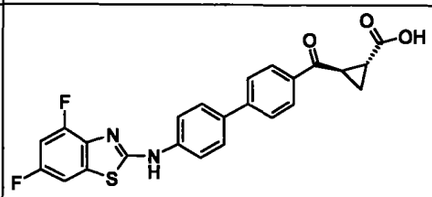
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96		ácido 2-{[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]carbonil}ciclopropan-carboxílico	415,2	3,21	1	B	mezcla trans racémica		
97		ácido 2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclohexan-carboxílico	491,2	3,90	1	B	mezcla trans racémica		

378

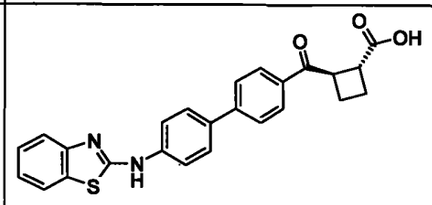
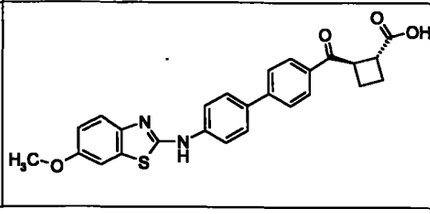
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98		ácido 2-({4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopropan-carboxílico	429,2	3,49	1	B	mezcla trans racémica		
99		ácido 2-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopropan-carboxílico	445,2	3,17	1	B	mezcla trans racémica		

348

379

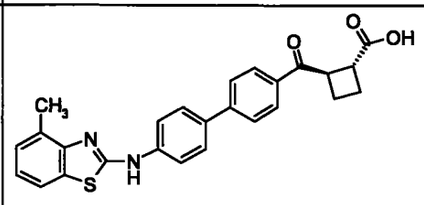
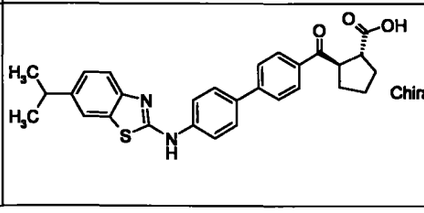
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
100		ácido 2-({4'-[(5,7-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopropan-carboxílico	451,1	3,53	1	B	mezcla trans racémica		
101		ácido 2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopropan-carboxílico	451,1	3,41	1	B	mezcla trans racémica		

380

No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
102		ácido 2-{[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]carbonil}ciclobutan-carboxílico	429,2	3,27	1	B	mezcla trans racémica		
103		ácido 2-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclobutan-carboxílico	459,2	3,42	1	B	mezcla trans racémica		

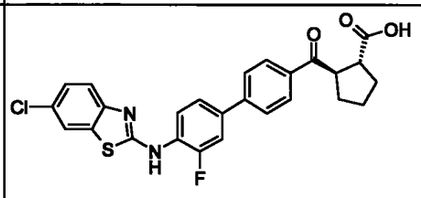
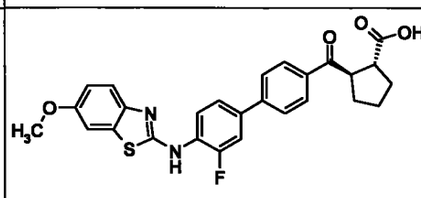
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381

No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
104		ácido 2-({4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclobutan-carboxílico	443,2	3,73	1	B	mezcla trans racémica		
105		ácido (1R,2R)-2-({4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	485,3	4,31	1	A	R,R-trans (de intermediario quiral)	90	

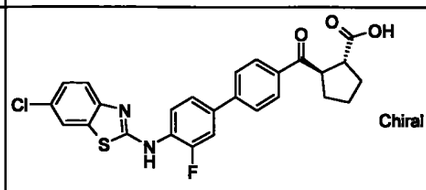
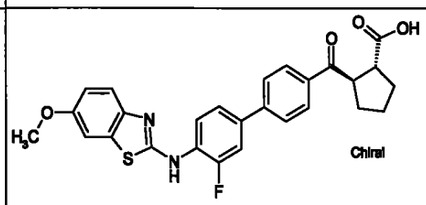
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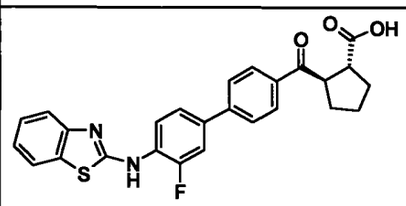
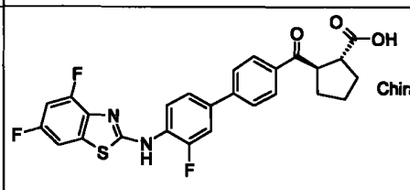
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
106		ácido 2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	495,1	3,91	2	B	mezcla trans racémica		
107		ácido 2-({3'-fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	491,1	3,77	2	B	mezcla trans racémica		

387

383

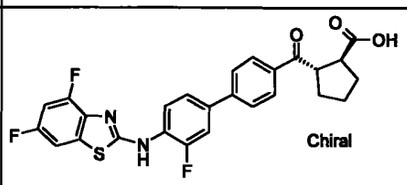
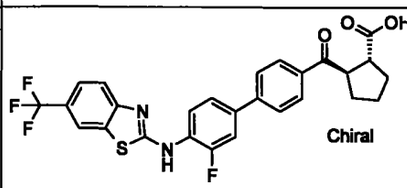
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
108		ácido (1R,2R)-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	495,3	4,01	1	A	R,R-trans (de intermediario quiral)	>99	18
109		ácido (1R,2R)-2-({3'-fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	491,3	3,56	1	B	R,R-trans (de intermediario quiral)	89	8

384

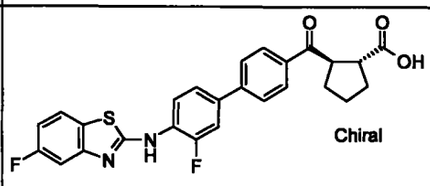
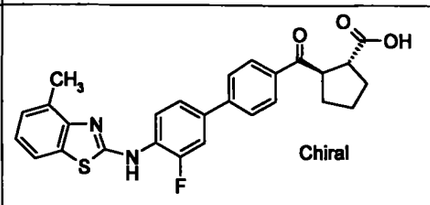
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
110		ácido 2-{[4'-(1,3-benzotiazol-2-ilamino)-3'-fluoro-1,1'-bifenil-4-il]carbonil}ciclopentan-carboxílico	461,4	3,60	1	B	mezcla trans racémica		
111		ácido (1R,2R)-2-{{4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	497,2	3,71	1	B	R,R-trans (de HPLC prep. quiral)	>99	

384

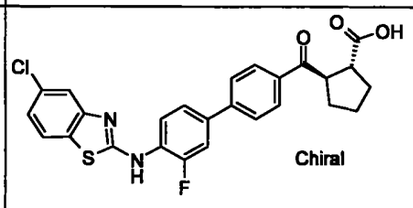
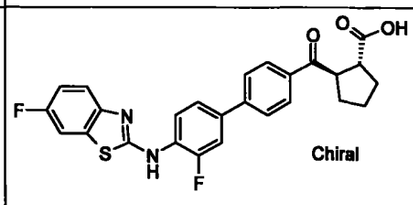
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
112		ácido (1S,2S)-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	497,2	3,71	1	B	S,S-trans (de HPLC prep. quiral)	95	
113		ácido (1R,2R)-2-[(3'-fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico	529,3	4,33	1	B	R,R-trans (de intermediario quiral)	97	

386

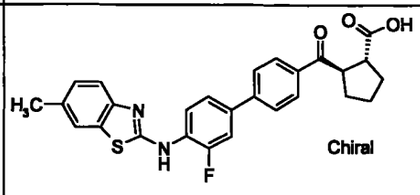
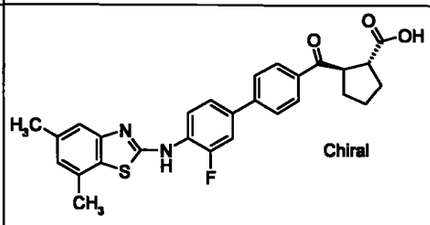
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
114		ácido (1R,2R)-2-({3'-fluoro-4'-[(5-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	479,3	4,10	1	B	R,R-trans (de intermediario quiral)	90	
115		ácido (1R,2R)-2-({3'-fluoro-4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	475,3	3,97	1	A	R,R-trans (de intermediario quiral)	83	21

387

No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
116		ácido (1R,2R)-2-({4'-[(5-cloro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	495,2	3,85	1	B	R,R-trans (de intermediario quiral)	96	
117		ácido (1R,2R)-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	479,3	3,64	1	A	R,R-trans (de intermediario quiral)	96	26

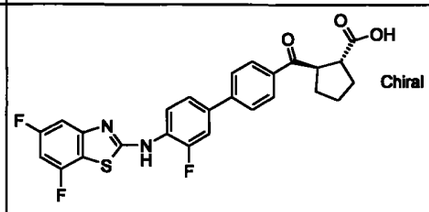
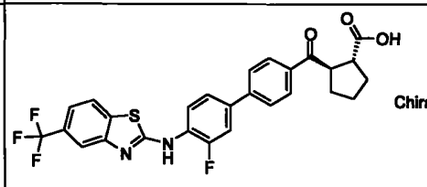
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
118		ácido (1R,2R)-2-({3'-fluoro-4'-[(6-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	475,3	3,71	1	B	R,R-trans (de HPLC prep. quiral)	90	
119		ácido (1R,2R)-2-({4'-[(5,7-dimetil-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	489,3	3,85	1	A	R,R-trans (de intermediario quiral)	66	

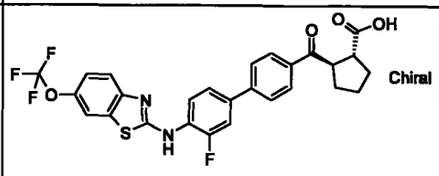
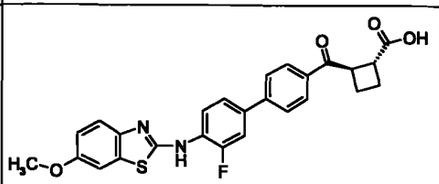
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389

No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
120		ácido (1R,2R)-2-({4'-[(5,7-difluoro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	497,2	3,84	1	A	R,R-trans (de intermediario quiral)	80	
121		ácido (1R,2R)-2-[(3'-fluoro-4'-{[5-(trifluorometil)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico	529,1	3,90	1	A	R,R-trans (de intermediario quiral)	90	

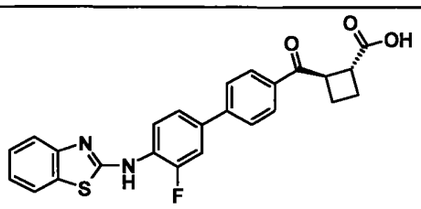
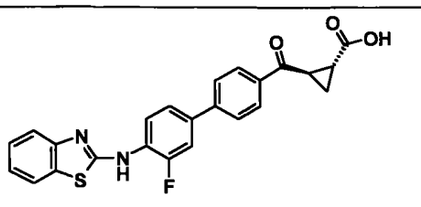
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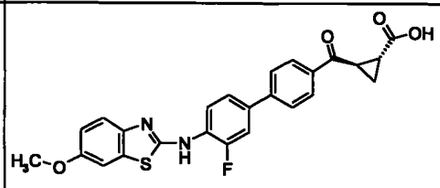
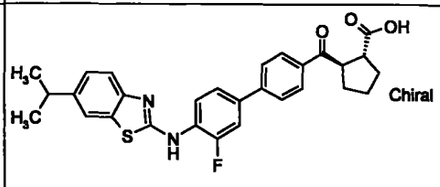
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
122	 Chiral	ácido (1R,2R)-2-[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico	545,3	3,93	1	A	R,R-trans (de intermediario quiral)	95	25
123		ácido 2-((3'-fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclobutan-carboxílico	477,2	3,54	1	A	mezcla trans racémica		

390

391

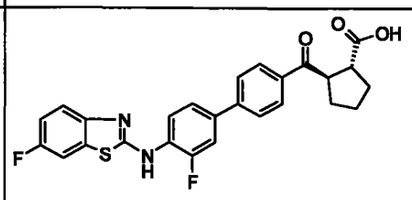
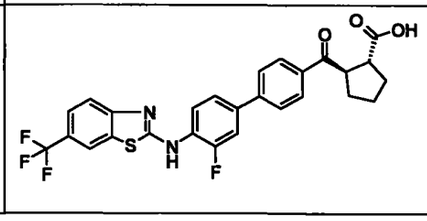
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
124		ácido 2-{[4'-(1,3-benzotiazol-2-ilamino)-3'-fluoro-1,1'-bifenil-4-il]carbonil}ciclobutan-carboxílico	447,1	3,56	1	A	mezcla trans racémica		
125		ácido 2-{[4'-(1,3-benzotiazol-2-ilamino)-3'-fluoro-1,1'-bifenil-4-il]carbonil}ciclopropan-carboxílico	433,2	3,31	1	A	mezcla trans racémica		

392

No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
126		ácido 2-({3'-. fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopropan-carboxílico	463,2	3,47	1	A	mezcla trans racémica		
127		ácido (1R,2R)-2-({3'-fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	503,3	4,46	1	A	R,R-trans (de intermediario quiral)	90	

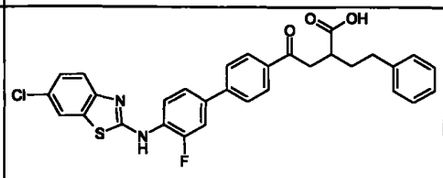
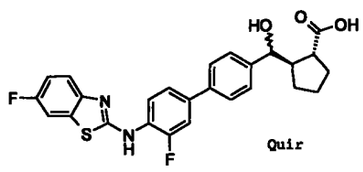
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No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
128		ácido 2-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico	479,3	3,65	1	B	mezcla trans racémica		
129		ácido 2-[(3'-fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico	529,3	3,89	1	A	mezcla trans racémica		

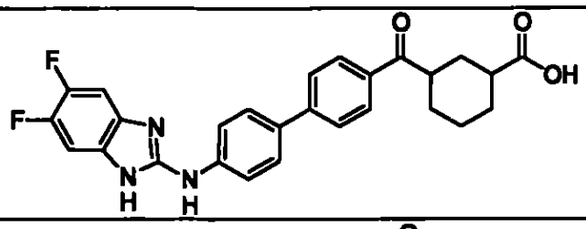
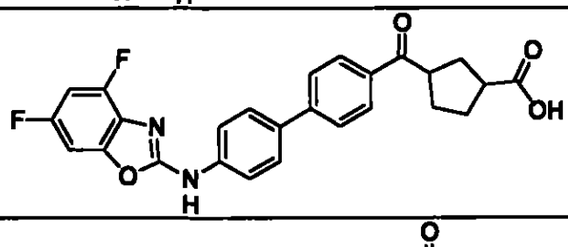
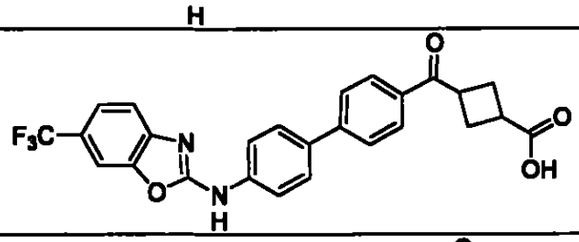
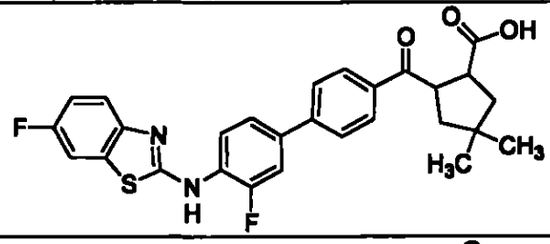
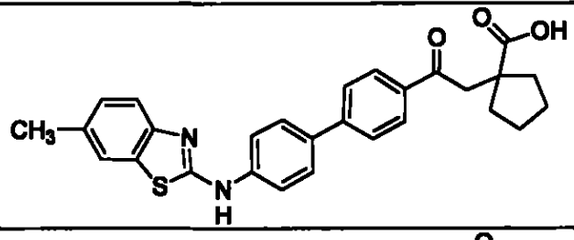
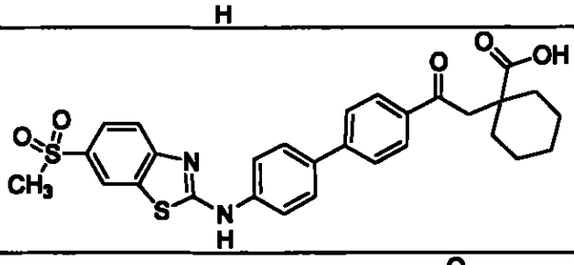
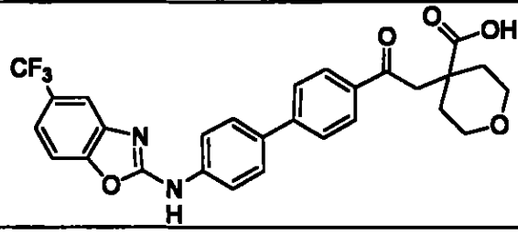
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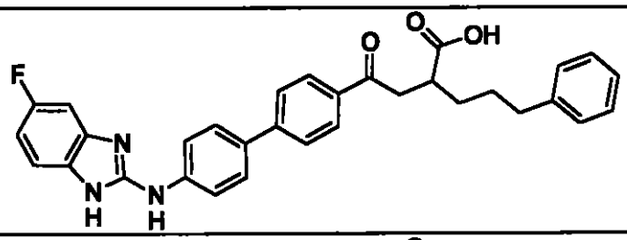
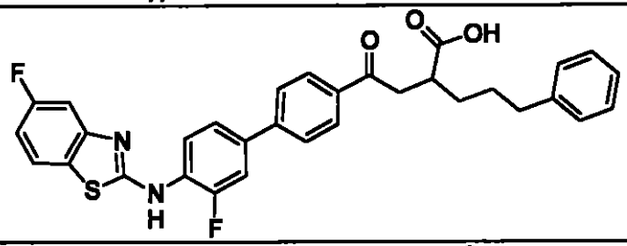
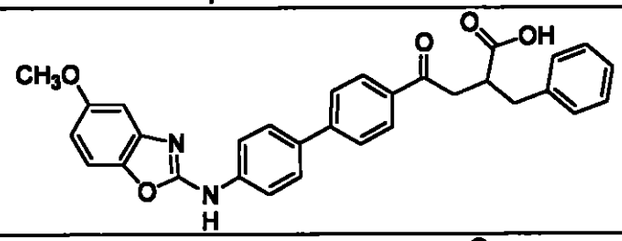
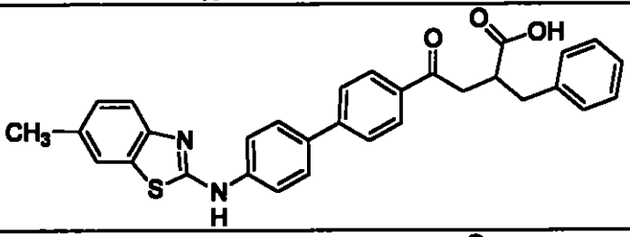
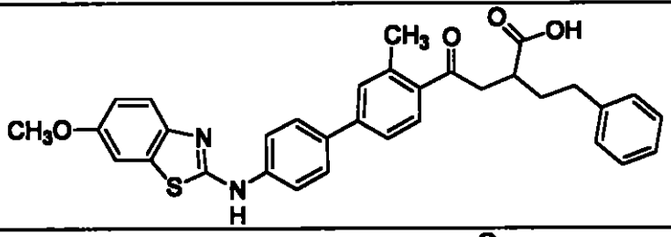
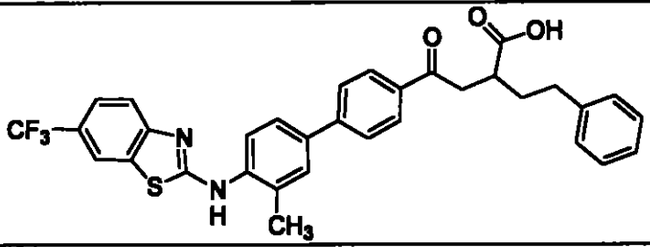
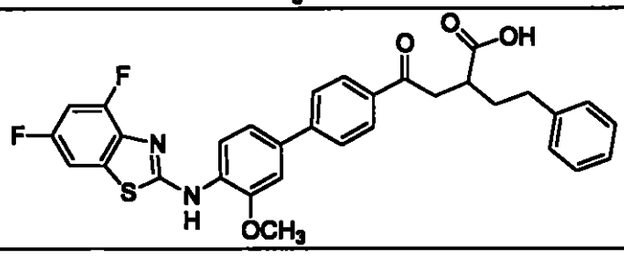
No. de Entrada	Estructura	Nombre de IUPAC	CL-EM m/z (MH+)	CL-EM ret. time (min)	Método de CL-EM	Vía de síntesis	Quiralidad y vía	% de ee	No. Ej. descrito en el texto
130		4-{4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}-4-oxo-2-(2-feniletil)butanoico ácido	559,2	4,13	1	A	mezcla racémica		
131	 Quir	ácido (1R,2R)-2-[{3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-bifenil-4-il}(hidroxi)-metil]-ciclopentan-carboxílico	481,3	Dos isómeros: 3.33 & 3.46	1	N/A	R,R-trans-ciclo-pentil (de intermediario quiral)		34

Mediante el uso de los métodos descritos anteriormente y seleccionando los materiales de partida apropiados, pueden realizarse otros compuestos de la invención y se ilustran en la Tabla 2 a continuación.

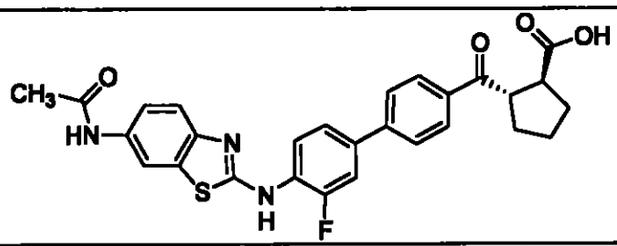
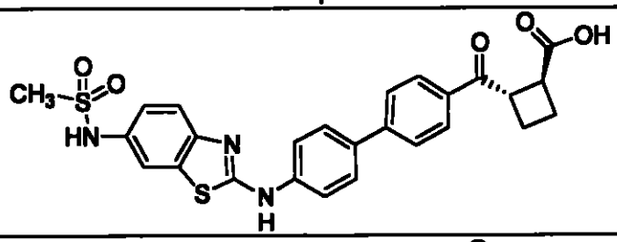
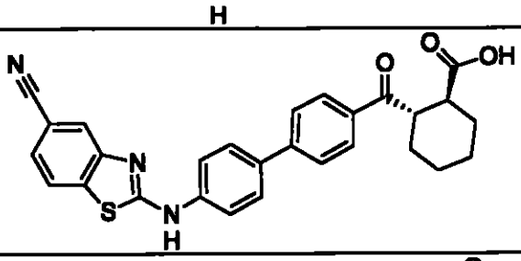
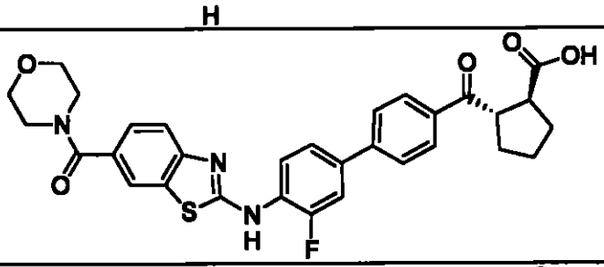
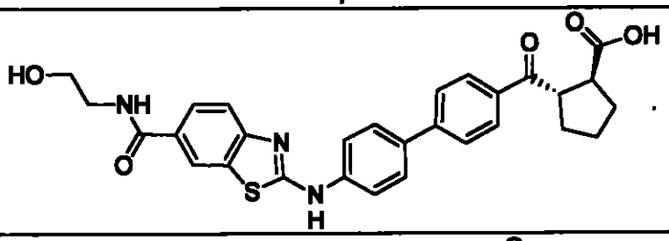
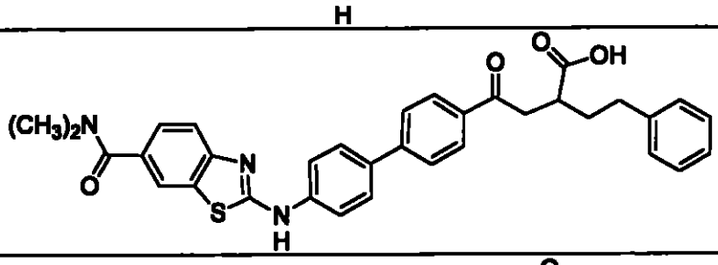
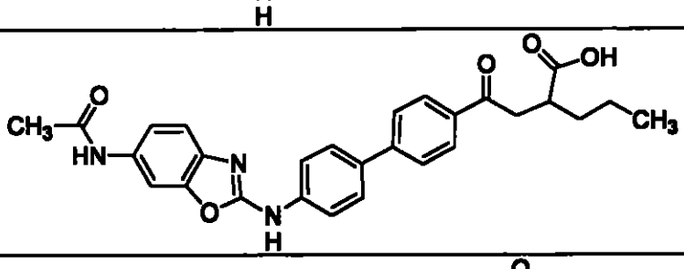
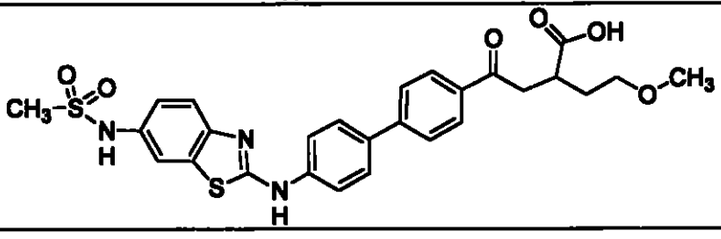
Tabla 2

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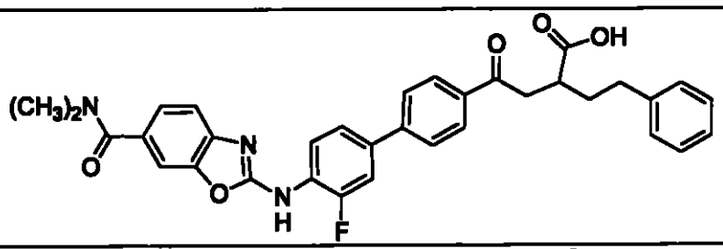
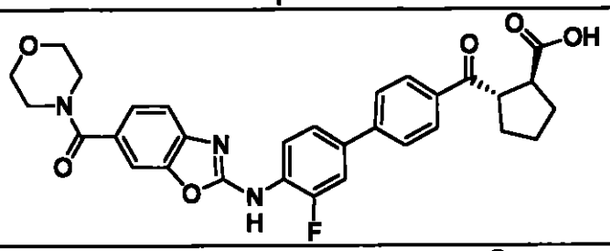
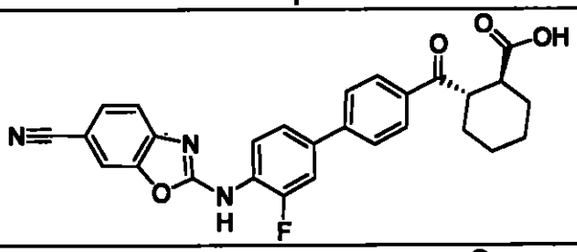
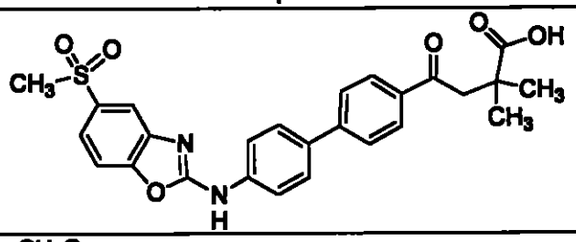
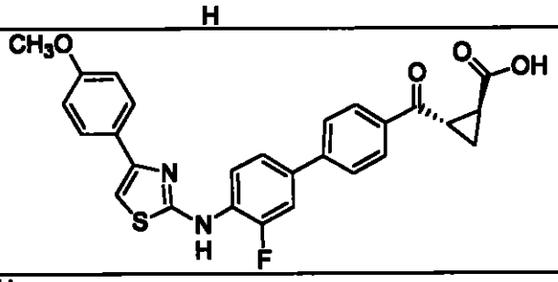
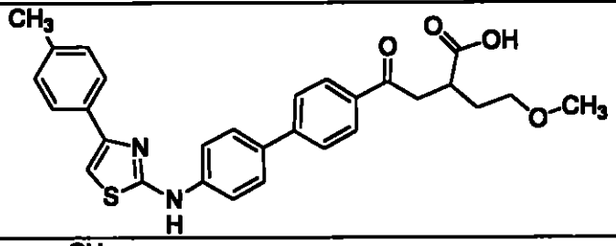
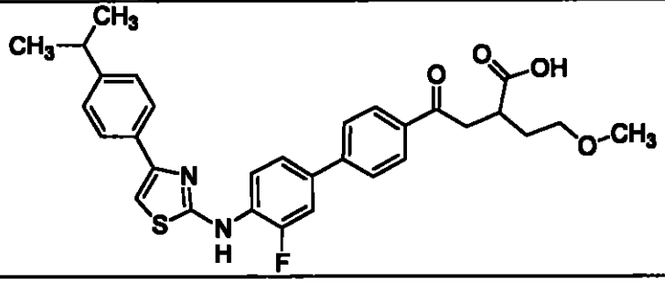
396

No. de Entrada	Estructura
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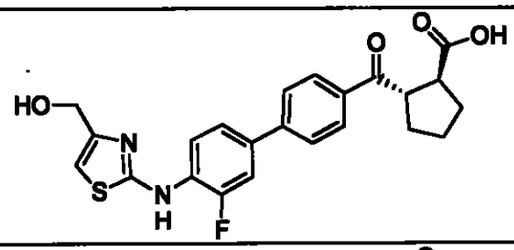
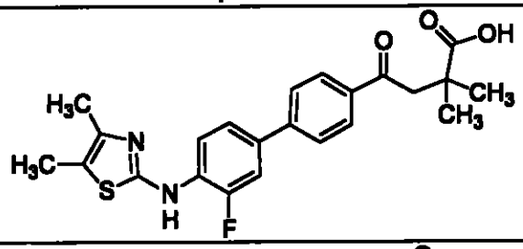
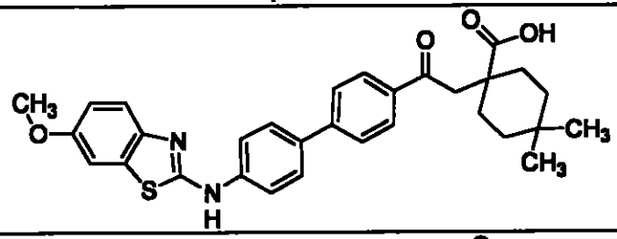
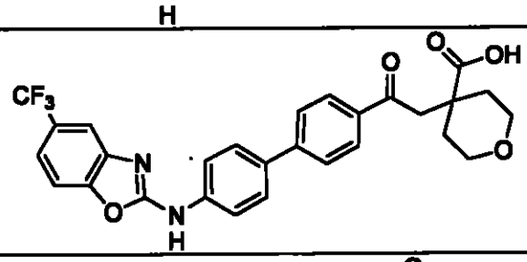
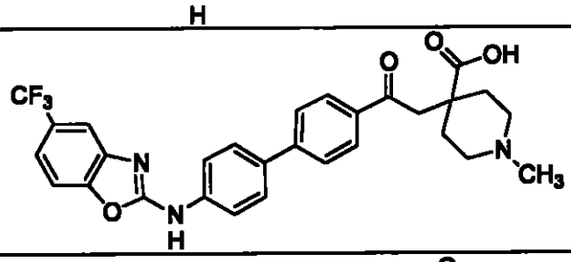
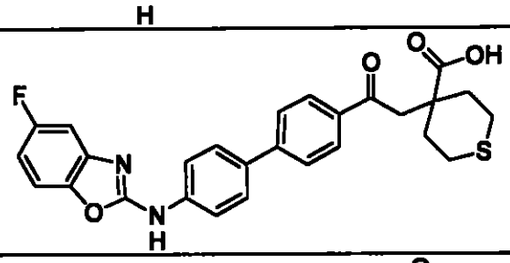
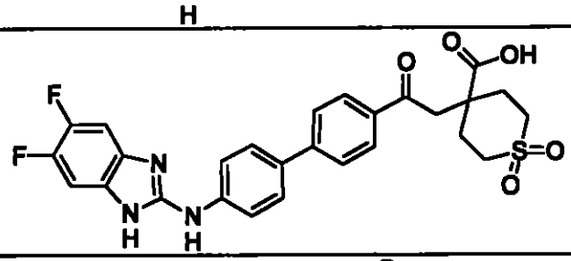
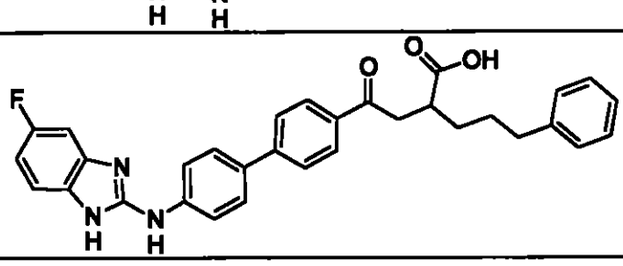
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No. de Entrada	Estructura
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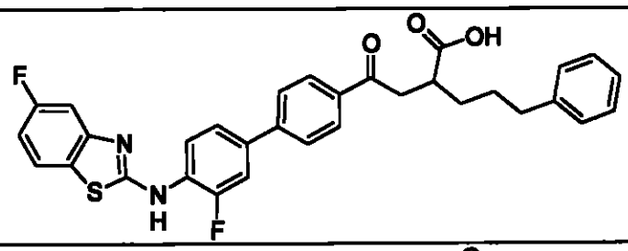
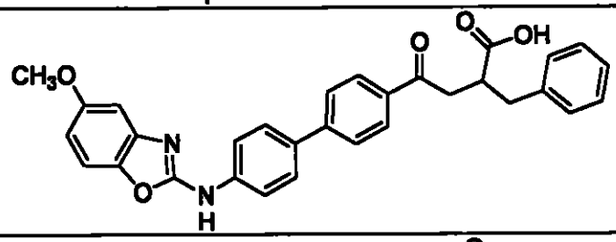
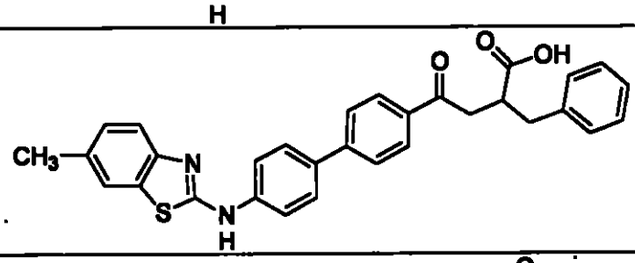
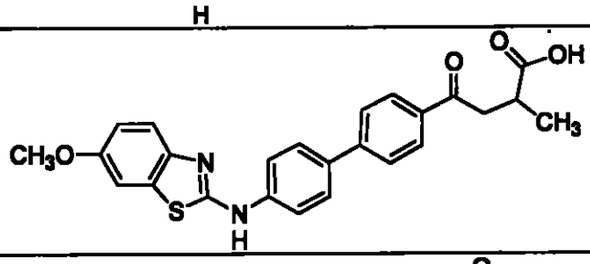
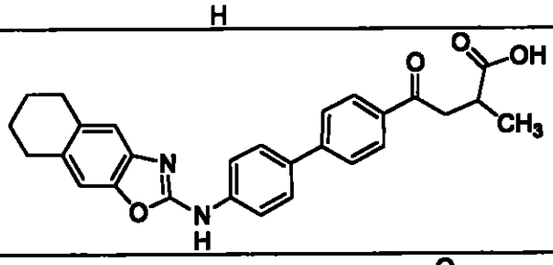
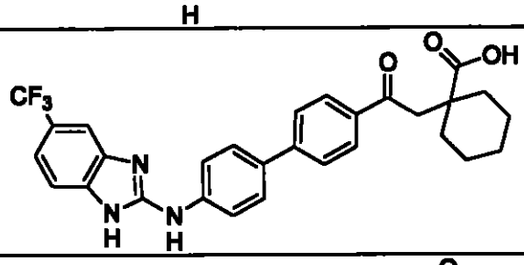
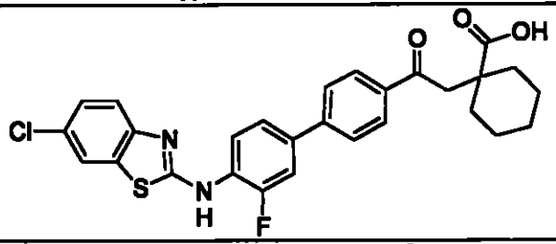
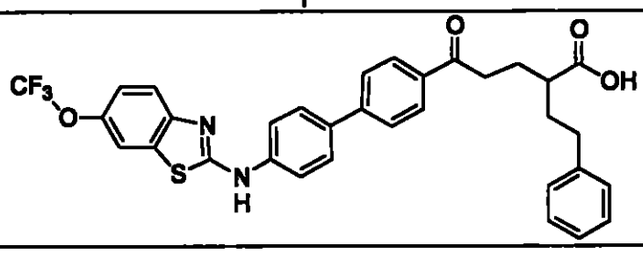
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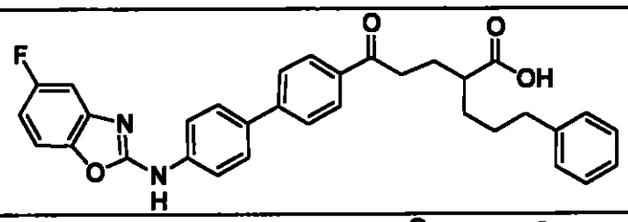
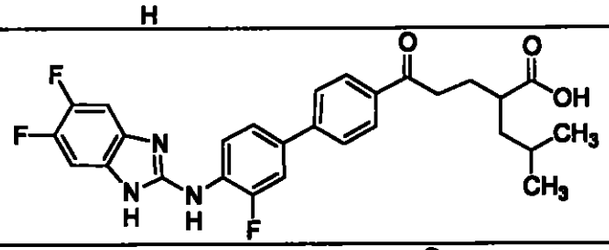
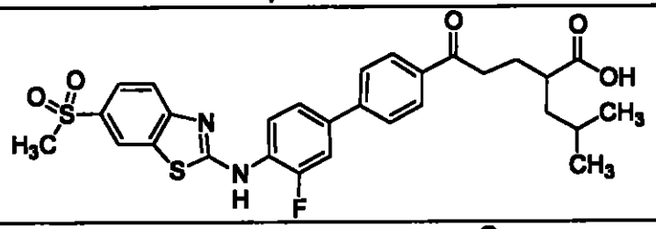
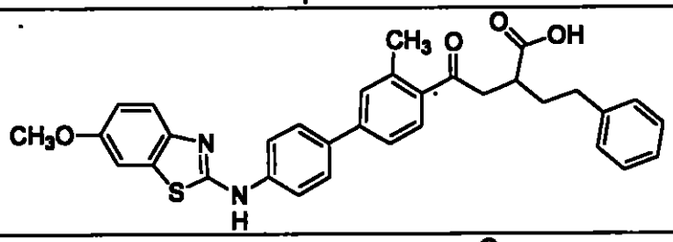
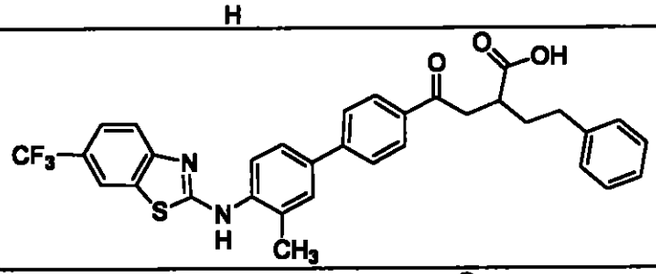
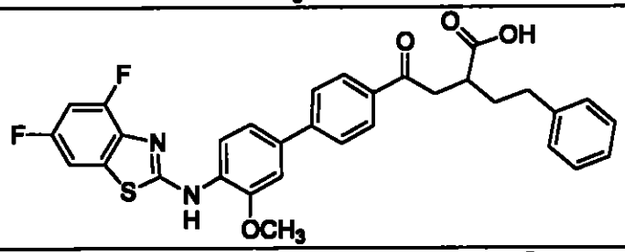
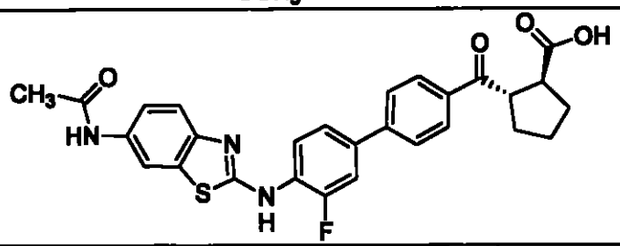
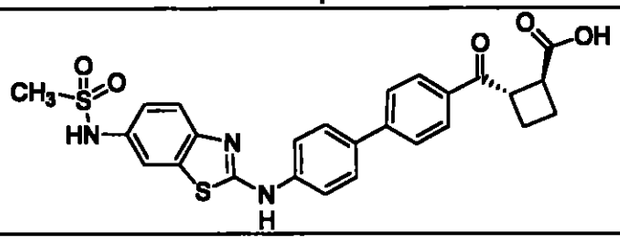
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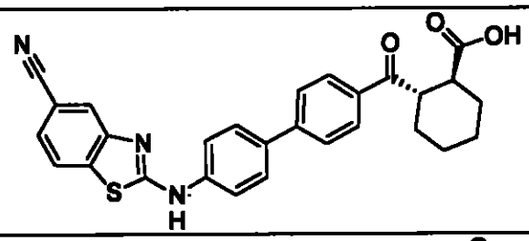
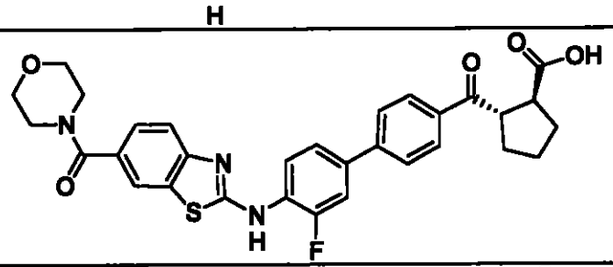
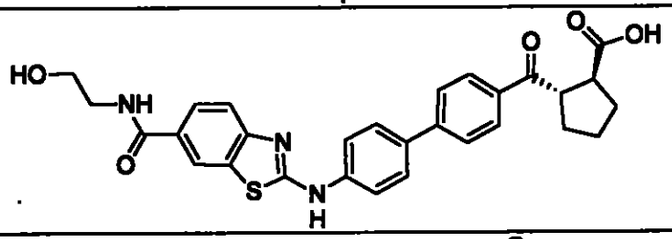
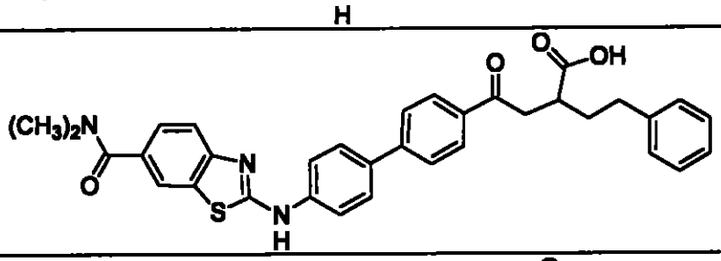
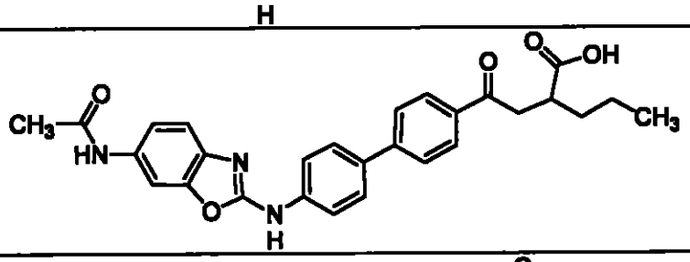
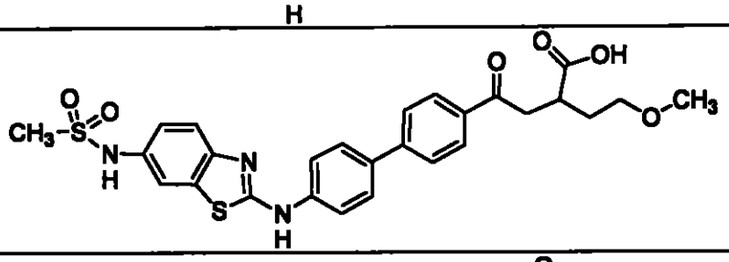
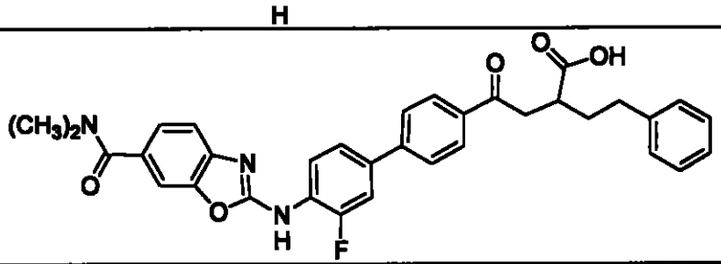
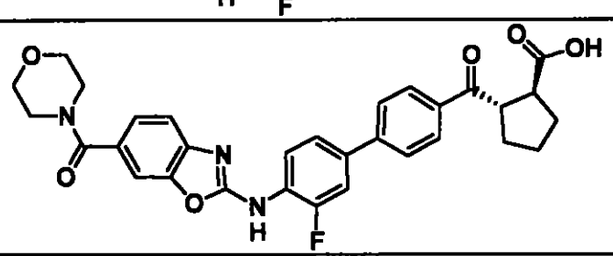
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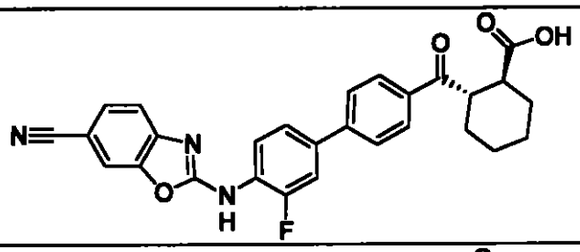
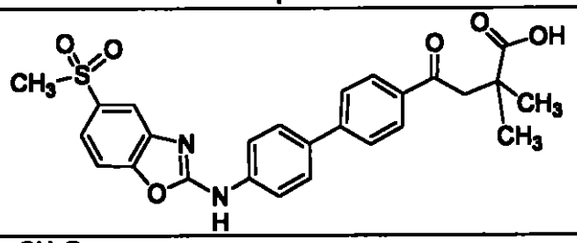
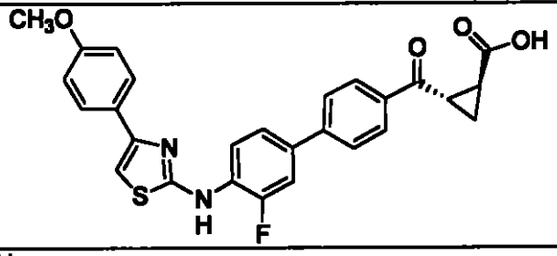
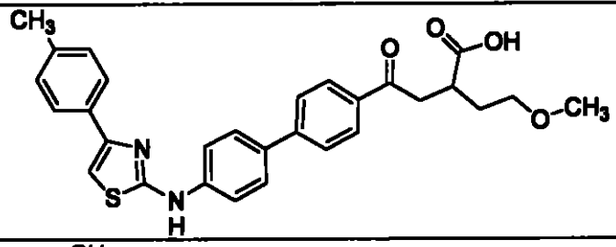
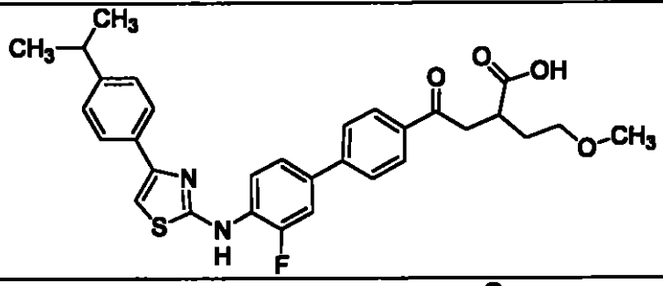
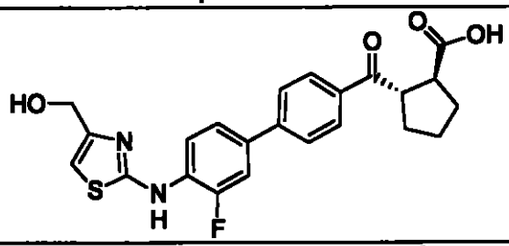
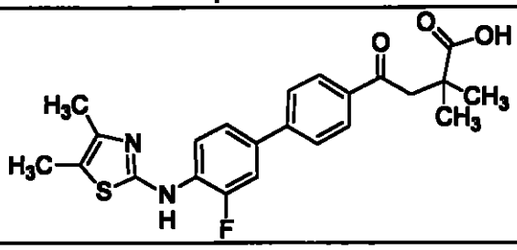
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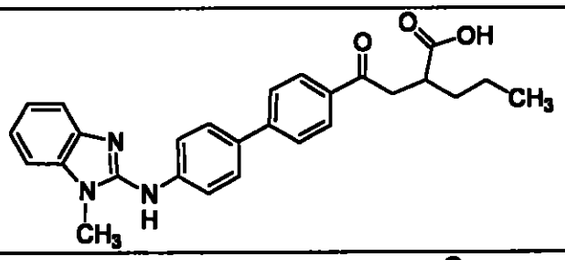
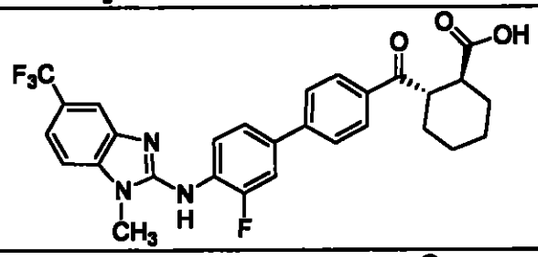
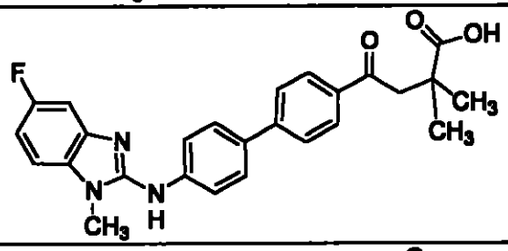
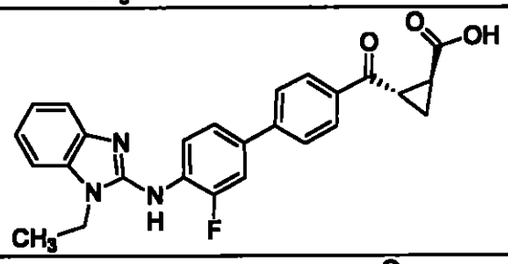
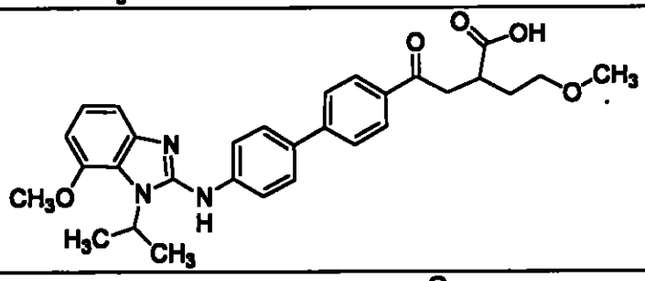
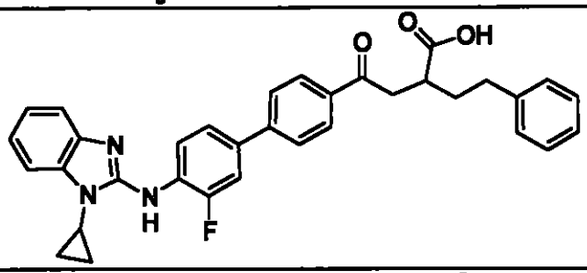
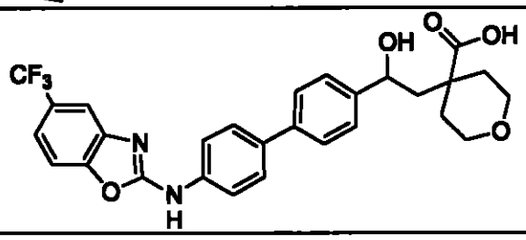
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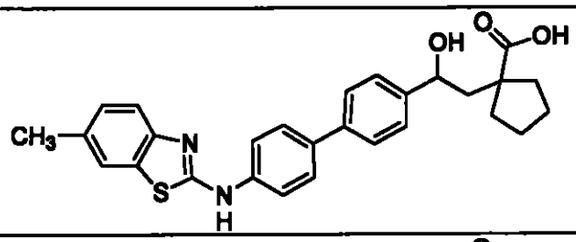
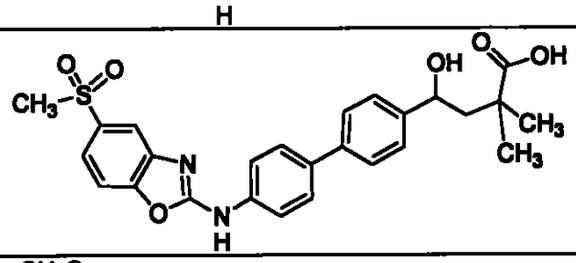
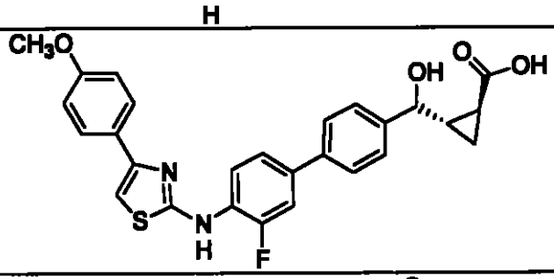
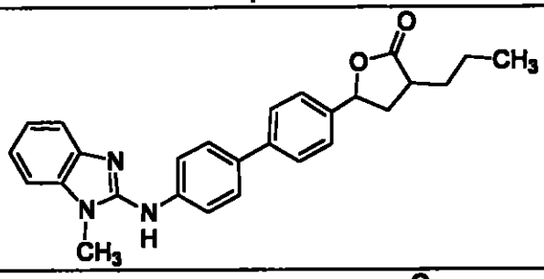
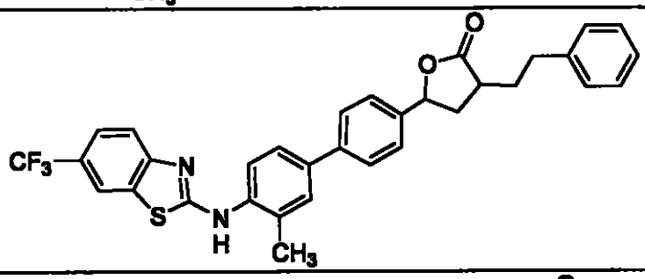
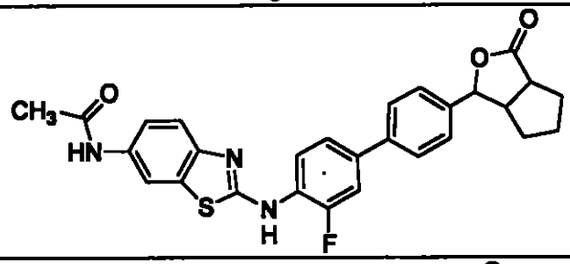
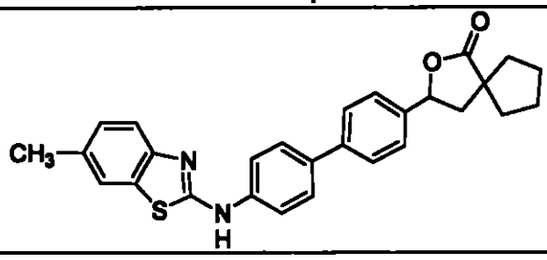
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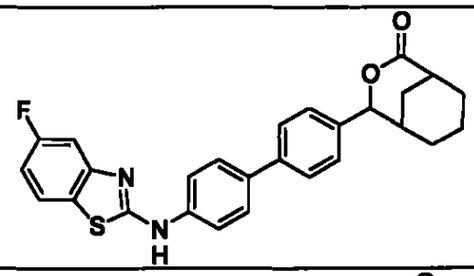
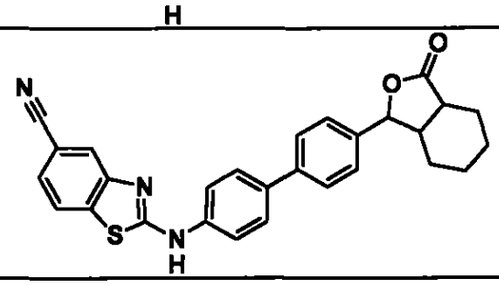
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Métodos de Uso

Como se usa aquí, los diferentes términos se definen a continuación.

Cuando se introducen los elementos de la presente invención o sus realizaciones preferidas, se pretende que los artículos "un," "una," "el/la," y "dicho/a" signifiquen que hay uno o más de un elemento. Se pretende que los términos "que comprende," "que incluye," y "que tiene" sean inclusivos y signifiquen que puede haber elementos adicionales distintos de los elementos enumerados.

El término "sujeto" como se usa aquí incluye mamíferos (por ej., humanos y animales).

El término "tratamiento" incluye cualquier proceso, acción, aplicación, terapia o similares, en el cual un sujeto, incluyendo un ser humano, recibe asistencia médica con el objeto de mejorar la afección del sujeto, directa o indirectamente, o demorar la progresión de una condición o trastorno en el sujeto.

El término "tratamiento combinado" o "tratamiento concomitante" significa la administración de dos o más agentes terapéuticos para tratar una afección y/o un trastorno diabético. Dicha administración abarca la administración concomitante de dos o más agentes en un modo sustancialmente simultáneo, tal como en una única cápsula que tiene una relación fija de ingredientes activos o en cápsulas múltiples, separadas para cada agente

inhibidor. Además, dicha administración abarca el uso de cada tipo de agente terapéutico en un modo secuencial.

La frase "terapéuticamente efectivo" significa la cantidad de cada agente administrado que logrará el objetivo de mejorar la gravedad de la afección diabética o el trastorno diabético, mientras que evita o minimiza los efectos colaterales con un tratamiento terapéutico dado.

El término "aceptables desde el punto de vista farmacéutico" significa que el producto es apropiado para usar en un producto farmacéutico.

Se espera que los compuestos de Fórmula (I), Fórmula (Ia), y Fórmula (Ib) de esta invención sean valiosos como agentes terapéuticos. En consecuencia, una realización de esta invención incluye un método de tratamiento de varias afecciones en un paciente (incluyendo los mamíferos) que comprende la administración a dicho paciente de una composición que contiene una cantidad del compuesto de Fórmula (I), Fórmula (Ia), o Fórmula (Ib) que es efectiva en el tratamiento de la afección pretendida.

Un objetivo de esta invención es suministrar métodos para el tratamiento de la obesidad e inducir la pérdida de peso en un individuo a través de la administración de un compuesto de la invención. El método de la invención comprende administrar a un individuo una cantidad terapéuticamente efectiva de por lo menos un compuesto de la invención, o uno de sus profármacos, que sea suficiente para inducir la pérdida de peso. La invención comprende, además, un método para prevenir la pérdida de peso en un individuo mediante la administración de una cantidad de por lo menos un compuesto de la invención, o uno de sus profármacos, que sea suficiente para prevenir la pérdida de peso.

La presente invención se refiere, además, al uso de los compuestos de esta invención para el tratamiento de enfermedades relacionadas con la obesidad incluyendo dislipidemia asociada y otras complicaciones relacionadas con la obesidad y el sobrepeso tales como, por ejemplo, colesterol, cálculos vesiculares, afección de la vesícula, gota, cáncer (por ej., cáncer de colon, recto, próstata, mama, ovarios, endometrio, cérvix, vesícula y conducto biliar), anormalidades menstruales, infertilidad, ovarios poliquísticos, osteopatía degenerativa, y apnea del sueño, como también para una cantidad de otros usos farmacéuticos asociados con éstos, tales como la regulación del apetito y la ingesta de alimentos, dislipidemia, hipertrigliceridemia,

Síndrome X, diabetes tipo 2 (diabetes no insulino dependiente), enfermedades ateroescleróticas tales como insuficiencia cardiaca, hiperlipidemia, hipercolesteremia, niveles bajos de HDL, hipertensión, enfermedad cardiovascular (incluyendo ateroesclerosis, insuficiencia coronaria, arteriopatía coronaria, e hipertensión), enfermedad cerebrovascular tal como accidente cerebrovascular, y enfermedad de los vasos periféricos. Los compuestos de esta invención pueden ser útiles, además, para tratar trastornos fisiológicos relacionados con, por ejemplo, la regulación de la sensibilidad a la insulina, respuesta inflamatoria, triglicéridos plasmáticos, los niveles de HDL, LDL y colesterol y similares.

Los compuestos de Fórmula (I), Fórmula (Ia), o Fórmula (Ib) pueden administrarse solos o combinados con uno o más agentes terapéuticos. El tratamiento combinado incluye la administración de una formulación de dosificación farmacéutica única que contiene un compuesto de Fórmula (I), Fórmula (Ia), o Fórmula (Ib) y uno o más agentes terapéuticos, como también la administración del compuesto de Fórmula (I), Fórmula (Ia), o Fórmula (Ib) y cada uno de los agentes terapéuticos individuales en su propia formulación de dosificación farmacéutica individual. Por ejemplo, un compuesto de Fórmula (I), Fórmula (Ia), o Fórmula (Ib) y un agente terapéutico pueden administrarse al paciente juntos en una composición de dosificación oral única tal como un comprimido o una cápsula, o cada agente puede administrarse en formulaciones de dosificación oral separadas.

En los casos en que se usen formulaciones de dosificación separadas, el compuesto de Fórmula (I), Fórmula (Ia), o Fórmula (Ib) y uno o más agentes terapéuticos pueden administrarse esencialmente en el mismo momento (por ej., en forma concurrente) o en etapas separadas (por ej., secuencialmente).

Por ejemplo, los compuestos de Fórmula (I), Fórmula (Ia), o Fórmula (Ib) pueden usarse en combinación con otros tratamientos y fármacos útiles para el tratamiento de la obesidad. Por ejemplo, los fármacos anti-obesidad incluyen agonistas β-3 tales como CL-316,243; agonistas CB-1; inhibidores del neuropéptido Y5; supresores del apetito, tales como, por ejemplo, sibutramina (Meridia); e inhibidores de lipasa, tales como, por ejemplo, orlistat (Xenical). Los compuestos de la presente invención pueden administrarse, además, en combinación con un compuesto farmacológico que modula la digestión

y/o el metabolismo, tales como fármacos que modulan la termogénesis, la lipólisis, la movilidad intestinal, la absorción de grasas y la saciedad.

Además, los compuestos de Fórmula (I), Fórmula (Ia), o Fórmula (Ib) pueden administrarse en combinación con uno o más de los siguientes agentes para el tratamiento de la diabetes o trastornos relacionados con la diabetes incluyendo ligandos PPAR (agonistas, antagonistas), secretagogos de insulina, por ejemplo, fármacos de sulfonilurea y secretagogos que no contienen sulfonilurea, inhibidores de α-glucosidasa, sensibilizadores de insulina, compuestos reductores de la producción de glucosa hepática, e insulina y derivados de la insulina. Dichos tratamientos pueden administrarse antes de, en forma concurrente con, o luego de la administración de los compuestos de la invención. La insulina y los derivados de la insulina incluyen formas y formulaciones de la insulina de acción prolongada y corta. Los ligandos PPAR pueden incluir agonistas y/o antagonistas de cualesquiera de los receptores de PPAR o sus combinaciones. Por ejemplo, los ligandos 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 PPAR incluyen, por ejemplo, rosiglitazona, troglitazona, y pioglitazona. Los fármacos de sulfonilurea incluyen, por ejemplo, gliburida, glimepirida, clorpropamida, tolbutamida, y glipizida. Los inhibidores de α-glucosidasa que pueden ser útiles en el tratamiento de la diabetes cuando se administran con un compuesto de la invención incluyen acarbosa, miglitol, y voglibosa. Los sensibilizadores de insulina que pueden ser útiles en el tratamiento de la diabetes incluyen agonistas de PPAR-γ tales como las glitazonas (por ej., troglitazona, pioglitazona, englitazona, MCC-555, rosiglitazona, y similares) y otros compuestos de tiazolidindiona y no tiazolidindiona; biguanidas tales como metformina y fenformina; inhibidores de la proteína fosfatasa tirosina-1B (PTP-1B); inhibidores de dipeptidil peptidasa IV (DPP-IV), y inhibidores de 11beta-HSD. Los compuestos reductores de la producción de glucosa hepática que pueden ser útiles en el tratamiento de la diabetes cuando se administran con un compuesto de la invención incluyen agonistas de glucagon y metformina, tales como Glucophage y Glucophage XR. Los secretagogos de insulina que pueden ser útiles en el tratamiento de la diabetes cuando se administran con

410.

un compuesto de la invención incluyen sulfonilurea y fármacos que no contienen sulfonilurea: GLP-1, GIP, PACAP, secretina, y sus derivados; nateglinida, meglitinida, repaglinida, glibenclamida, glimepirida, clorpropamida, glipizida. El GLP-1 incluye derivados de GLP-1 con vidas medias más largas que los GLP-1 originales, tales como, por ejemplo, GLP-1 derivado de ácido graso y exendina.

Los compuestos de la invención pueden usarse, además, en los métodos de la invención en combinación con fármacos usados comúnmente para tratar los trastornos lipídicos en los pacientes. Dichos fármacos incluyen, sin carácter limitativo, inhibidores de la reductasa HMG-CoA, ácido nicotínico, compuestos reductores de ácidos grasos (por ej., acipimox); fármacos reductores de lípidos (por ej., estanol ésteres, esterol glicosidas tales como tiquesida, y azetidinonas tales como ezetimibe), inhibidores de ACAT (tales como avasimibe), secuestradores de ácido biliar, inhibidores de la recaptación de ácido biliar, inhibidores del transporte microsómico de triglicéridos, y derivados de ácido fíbrico. Los inhibidores de la reductasa HMG-CoA incluyen, por ejemplo, lovastatina, simvastatina, pravastatina, fluvastatina, atorvastatina, rivastatina, itavastatina, cerivastatina, y ZD-4522. Los derivados de ácido fíbrico incluyen, por ejemplo, clofibrato, fenofibrato, bezafibrato, ciprofibrato, beclofibrato, etofibrato, y gemfibrozil. Los secuestradores incluyen, por ejemplo, colestiramina, colestipol, y derivados de dialquilaminoalquilo de dextran entrecruzado.

Los compuestos de la invención pueden usarse, además, en combinación con fármacos contra la hipertensión, tales como, por ejemplo, bloqueadores β e inhibidores de ACE. Ejemplos de los agentes anti-hipertensivos agregados para usar en combinación con los compuestos de la presente invención incluyen bloqueadores del canal de calcio (tipo L- y tipo T-; por ej., diltiazem, verapamil, nifedipina, amlodipina y mybefradil), diuréticos (por ej., clorotiazida, hidroclorotiazida, flumetiazida, hidroflumetiazida, bendroflumetiazida, metilclorotiazida, triclorometiazida, politiazida, benztiazida, ácido etacrínico tricrinafeno, clortalidona, furosemida, musolimina, bumetanida, triamtreneno, amilorida, espironolactona), inhibidores de renina, inhibidores de ACE (por ej., captopril, zofenopril, fosinopril,

enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), antagonistas del receptor AT-1 (por ej., losartan, irbesartan, valsartan), antagonistas del receptor ET (por ej., sitaxsentan, atrsentan, inhibidores de la endopeptidasa neutra (NEP), inhibidores de basopepsidasa (inhibidores duales de NEP-ACE) (por ej., omapatrilat y gemopatrilat), y nitratos.

Los compuestos de Fórmula (I), Fórmula (Ia), y Fórmula (Ib) pueden utilizarse, además, en forma de base libre o en composiciones, como también en investigación y diagnóstico o como estándares de referencia analítica, y similares, que son conocidos en el arte. Por consiguiente, la presente invención incluye composiciones que están formadas por un vehículo inerte y una cantidad efectiva de un compuesto de Fórmula (I), Fórmula (Ia), o Fórmula (Ib), o una de sus sales o uno de sus ésteres. Un vehículo inerte es cualquier material que no interactúa con el compuesto que debe transportarse y que brinda soporte, medio de transporte, granel, material rastreable, y similares al compuesto que debe transportarse. Una cantidad efectiva del compuesto es aquella cantidad que produce un resultado o ejerce una influencia sobre el procedimiento particular realizado.

Se anticipa que las formas de profármacos de los compuestos de esta invención demostrarán su utilidad en ciertas circunstancias, y se pretende que dichos compuestos también caigan dentro del alcance de la invención. Las formas de profármacos pueden tener ventajas por sobre los compuestos de origen ejemplificados aquí, en el sentido que se absorben mejor, se distribuyen mejor, penetran más fácilmente en el sistema nervioso central, se metabolizan o depuran más lentamente, etc. Las formas de profármacos también pueden tener ventajas de formulación en lo que respecta a la cristalinidad o solubilidad en agua. Por ejemplo, los compuestos de la invención que tienen uno o más grupos hidroxilo pueden convertirse en ésteres que llevan uno o más grupos carboxilo, hidroxilo o amino, que se hidrolizan a valores de pH fisiológico o se rompen con las esterasas o lipasas endógenas *in vivo* (*ver, por ej.*, Patentes de los Estados Unidos Nos. 4.942.184; 4.960.790; 5.817.840; y 5.824.701, todas incorporadas aquí a modo de referencia en su totalidad, como las referencias citadas en ellas).

412

Composiciones Farmacéuticas

En base a las pruebas anteriores u otros ensayos conocidos usados para determinar la eficacia para el tratamiento de las afecciones identificadas con anterioridad en los mamíferos, y comparando estos resultados con los resultados de medicamentos conocidos que se usan para tratar estas afecciones, la dosificación efectiva de los compuestos de esta invención puede determinarse ampliamente para el tratamiento de cada indicación deseada. La cantidad de ingrediente activo que se administrará en el tratamiento de una de estas afecciones puede variar ampliamente de acuerdo con consideraciones tale como el compuesto particular y la unidad de dosificación empleados, el modo de administración, el período de tratamiento, la edad y el sexo del paciente tratado, y la naturaleza y la extensión de la afección tratada.

La cantidad total de ingrediente activo que se administrará variará, en general, desde aproximadamente 0,001 mg/kg hasta aproximadamente 200 mg/kg, y con preferencia desde aproximadamente 0,01 mg/kg hasta aproximadamente 200 mg/kg de peso corporal por día. Una dosificación unitaria puede contener desde aproximadamente 0,05 mg hasta aproximadamente 1500 mg de ingrediente activo, y puede administrarse una o más veces por día. La dosificación diaria para administrar por inyección, incluyendo inyecciones endovenosas, intramusculares, subcutáneas y parenterales, y el uso de técnicas de infusión pueden ser desde aproximadamente 0,01 hasta aproximadamente 200 mg/kg. La dosificación rectal diaria puede ser desde 0,01 hasta 200 mg/kg de peso corporal total. La concentración transdérmica puede ser a requerida para mantener una dosificación diaria de desde 0,01 hasta 200 mg/kg.

Por supuesto, el régimen de dosificación inicial específico y continuo para cada paciente variará de acuerdo con la naturaleza y la gravedad de la afección, según el criterio del médico que diagnostica, la actividad del compuesto específico empleado, la edad del paciente, la dieta del paciente, la hora de administración, la vía de administración, la velocidad de excreción del fármaco, combinaciones farmacológicas, y similares. El modo de tratamiento deseado y el número de dosis de un compuesto de la presente invención o una de sus sales aceptables desde el punto de vista farmacéutico pueden ser determinados por aquellos expertos en el arte usando pruebas de tratamiento convencionales.

Los compuestos de esta invención pueden utilizarse para lograr el efecto

farmacológico deseado mediante la administración a un sujeto que lo necesita en una composición farmacéutica formulada de un modo apropiado. Un sujeto, por ejemplo, puede ser un mamífero, incluyendo un humano, que necesita tratamiento para una afección o enfermedad particular. Por consiguiente, la presente invención incluye composiciones farmacéuticas que están formadas por un vehículo aceptable desde el punto de vista farmacéutico y una cantidad efectiva desde el punto de vista farmacéutico de un compuesto identificado por los métodos descritos aquí, o una de sus sales o uno de sus ésteres aceptables desde el punto de vista farmacéutico. Un vehículo aceptable desde el punto de vista farmacéutico es cualquier vehículo que sea relativamente no tóxico e inocuo para un paciente en concentraciones consistentes con la actividad efectiva del ingrediente activo, de modo tal que cualquier efecto colateral atribuible al vehículo no vicie los efectos beneficiosos del ingrediente activo. Una cantidad efectiva desde el punto de vista farmacéutico de un compuesto es aquella cantidad que produce un resultado o ejerce una influencia sobre la afección particular tratada. Los compuestos identificados por los métodos descritos aquí pueden administrarse con un vehículo aceptable desde el punto de vista farmacéutico usando cualquier forma unitaria de dosificación convencional que resulte efectiva, incluyendo, por ejemplo, preparaciones de liberación inmediata y programada, por vía oral, parenteral, tópica, o similares.

Para administración oral, los compuestos pueden formularse en preparaciones sólidas o líquidas tales como, por ejemplo, cápsulas, píldoras, comprimidos, pastillas, grageas, fusiones, polvos, soluciones, suspensiones, o emulsiones, y pueden prepararse de acuerdo con métodos conocidos en el arte para la fabricación de composiciones farmacéuticas. Las formas sólidas de dosificación unitaria pueden ser una cápsula que puede ser del tipo común de gelatina con recubrimiento duro o blando que contiene, por ejemplo, tensioactivos, lubricantes, y rellenos inertes tales como lactosa, sacarosa, fosfato de calcio, y almidón de maíz.

En otra realización, los compuestos de esta invención pueden tomar forma de comprimidos con bases convencionales para comprimidos tales como lactosa, sacarosa, y almidón de maíz en combinación con aglutinantes tales como acacia,

almidón de maíz, o gelatina; agentes de desintegración para ayudar en la ruptura y disolución del comprimido luego de la administración tales como almidón de papa, ácido algínico, almidón de maíz, y goma guar; lubricantes que tienen la finalidad de mejorar el flujo de la granulación del comprimido y prevenir la adhesión del material del comprimido a las superficies de los colorantes y orificios del comprimido, por ejemplo, talco, ácido esteárico, o estearato de magnesio, calcio o zinc; colorantes; agentes de color; y agentes saborizantes que tienen como finalidad potenciar las calidades estéticas de los comprimidos y hacerlos más aceptables para el paciente. Los excipientes apropiados para usar en formas de dosificación oral líquidas incluyen diluyentes tales como agua y alcoholes, por ejemplo, etanol, alcohol bencílico, y alcoholes de polietileno, ya sea con o sin el agregado de un tensioactivo, agente de suspensión o agente emulsionante aceptables desde el punto de vista farmacéutico. Varios otros materiales pueden estar presentes como recubrimientos o para modificar de otro modo la forma física de la unidad de dosificación. Por ejemplo, los comprimidos, las píldoras o las cápsulas pueden estar recubiertos con laca, azúcar o ambos.

Los polvos y gránulos dispersables son apropiados para la preparación de una suspensión acuosa. Éstos suministran el ingrediente activo mezclado con un agente dispersante o humectante, un agente de suspensión, y uno o más preservantes. Los agentes de dispersión y humectantes apropiados se ejemplifican con aquellos ya mencionados con anterioridad. Además, pueden estar presentes excipientes adicionales, por ejemplo, aquellos agentes edulcorantes, saborizantes y colorantes descritos con anterioridad.

Las composiciones farmacéuticas de esta invención también pueden encontrarse en forma de emulsiones de aceite en agua. La fase de aceite puede ser un aceite vegetal tal como parafina líquida o una mezcla de aceites vegetales. Los agentes emulsionantes apropiados pueden ser (1) gomas de origen natural tales como goma acacia y goma tragacanto, (2) fosfatidas de origen natural tales como poroto y lecitina de soja, (3) ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato sorbitano, y (4) productos de condensación de dichos ésteres parciales con óxido de etileno, por ejemplo, monooleato sorbitano de

polioxietileno. Las emulsiones pueden contener, además, agentes edulcorantes y saborizantes.

Las suspensiones oleosas pueden formularse suspendiendo el ingrediente activo en un aceite vegetal tal como, por ejemplo, aceite de arachis, aceite de oliva, aceite de sésamo, o aceite de coco; o en un aceite mineral tal como parafina líquida. Las suspensiones oleosas pueden contener un agente aglutinante tal como, por ejemplo, cera de abejas, parafina líquida o alcohol cetílico. Las suspensiones pueden contener, además, uno o más preservantes, por ejemplo, p-hidroxibenzoato de etilo o *n*-propilo; uno o más agentes colorantes; uno o más agentes saborizantes; y uno o más agentes edulcorantes tales como sacarosa o sacarina.

Los jarabes y elixires pueden formularse con agentes edulcorantes tales como, por ejemplo, glicerol, propilenglicol, sorbitol, o sacarosa. Dichas formulaciones pueden contener, además, un demulcente, y agentes preservantes, saborizantes y colorantes.

Los compuestos de esta invención pueden administrarse, además, por vía parenteral, es decir, subcutánea, endovenosa, intramuscular o intraperitoneana, como formas farmacéuticas inyectables del compuesto en un diluyente fisiológicamente aceptable con un vehículo farmacéutico que puede ser un líquido o mezcla de líquidos estériles tales como agua, solución salina, dextrosa acuosa y soluciones azucaradas relacionadas; un alcohol tal como etanol, isopropanol, o hexadecil alcohol; glicoles tales como propilenglicol o polietilenglicol; glicerol cetales tales como 2,2-dimetil-1,1-dioxolan-4-metanol, éteres tales como poli(etileneglicol) 400; un aceite; un ácido graso, un éster de ácido graso o un glicérido; o un glicérido de ácido graso acetilado con o sin el agregado de un tensioactivo aceptable desde el punto de vista farmacéutico tal como un jabón o un detergente, agentes de suspensión tales como pectina, carbómeros, meticelulosa, hidroxipropilmetilcelulosa, o carboximetilcelulosa, o un agente emulsionante y otros adyuvantes farmacéuticos.

Son ilustrativos de aceites que pueden utilizarse en las formulaciones parenterales de esta invención aquellos de origen de petróleo, animal, vegetal, o sintético, por ejemplo, aceite de maní, aceite de poroto de soja,

aceite de sésamo, aceite de semilla de algodón, aceite de maíz, aceite de oliva, vaselina, y aceite mineral. Los ácidos grasos apropiados incluyen ácido oleico, ácido esteárico, y ácido isoesteárico. Los ésteres de ácidos grasos apropiados son, por ejemplo, oleato de etilo y miristato de isopropilo. Los jabones apropiados incluyen sales de metal alcalino graso, de amonio y trietanolamina y los detergentes apropiados incluyen detergentes catiónicos, por ejemplo, haluros de dimetil dialquil amonio, haluros de alquil piridinio, y acetatos de alquilamina; detergentes aniónicos, por ejemplo, alquil, aril, y olefin sulfonatos, alquil, olefin, éter, y sulfatos de monoglicéridos, y sulfosucinatos; detergentes no iónicos, por ejemplo, óxidos de amina grasa, alcanolamidas de ácido graso, y copolímeros de polioxietileno-polipropileno; y detergentes anfotéricos, por ejemplo, alquil-beta-aminopropionatos, y sales de amonio cuaternario de 2-alquilimidazolinas, como también sus mezclas.

Las composiciones parenterales de esta invención pueden contener normalmente desde aproximadamente 0,5% hasta aproximadamente 25% en peso del ingrediente activo en solución. Además, pueden usarse preservantes y buffers con resultados ventajosos. Para minimizar o eliminar la irritación en el sitio de inyección, dichas composiciones pueden contener un tensioactivo no iónico que tiene un balance hidrofílico-lipofílico (HLB) de desde aproximadamente 12 hasta aproximadamente 17. La cantidad de tensioactivo en dicha formulación varía desde aproximadamente 5% hasta aproximadamente 15% en peso. El tensioactivo puede ser un componente único que tiene el HLB anterior o puede ser una mezcla de dos o más componentes que tienen el HLB deseado.

Son ilustrativos de los tensioactivos usados en las formulaciones parenterales la clase de ésteres de ácido graso sorbitano, por ejemplo, monooleato sorbitano, y los aductos de peso molecular alto del óxido de etileno con una base hidrofóbica, formados por condensación del óxido de propileno con propilenglicol.

Las composiciones farmacéuticas pueden encontrarse en forma de suspensiones acuosas inyectables estériles. Dichas suspensiones pueden formularse de acuerdo con métodos conocidos usando agentes dipersantes o humectantes apropiados tales como, por ejemplo, carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetil-celulosa, alginato de sodio,

417

polivinilpirrolidona, goma tragacanto y goma acacia; agentes dispersantes o humectantes que pueden fosfatidas naturales tales como lecitina, un producto de condensación de un óxido de alquileno con un ácido graso, por ejemplo, estearato de polioxietileno, un producto de condensación de óxido de etileno con un alcohol alifático de cadena larga, por ejemplo, heptadecaetilenoxicetanol, un producto de condensación de óxido de etileno con un éster parcial derivado de un ácido graso y un hexitol tal como polioxietilen sorbitol monooleato, o un producto de condensación de un óxido de etileno con un éster parcial derivado de un ácido graso y un anhídrido de hexitol, por ejemplo polioxietilen sorbitan monooleato.

La preparación inyectable estéril también puede ser una solución o suspensión inyectable en un diluyente o solvente no tóxico aceptable para uso parenteral. Los diluyentes y solventes que también pueden emplearse son, por ejemplo, agua, solución de Ringer, y solución isotónica de cloruro de sodio. Además, se emplean convencionalmente aceites estériles fijos como solventes o medios de suspensión. Para este fin, puede emplearse cualquier aceite fijo, blando incluyendo mono o diglicéridos sintéticos. Además, pueden usarse también ácidos grasos como el ácido oleico en la preparación de injectables.

Una composición de la invención pueden administrarse, además, en forma de supositorios para administración rectal del fármaco. Estas composiciones pueden prepararse mezclando el fármaco con un excipiente apropiado que no produzca irritación que sea sólido a temperaturas normales pero líquido a la temperatura rectal y por consiguiente se fundirá en el recto para liberar el fármaco. Dichos materiales son, por ejemplo, manteca de cacao y polietilenglicol.

Otra formulación empleada en los métodos de la presente invención emplea dispositivos de administración transdérmica ("parches"). Dichas parches pueden usarse para suministrar infusión continua o discontinua de los compuestos de la presente invención en cantidades controladas. La construcción y el uso de parches transdérmicos para la administración de agentes farmacéuticos se conocen en el arte (*ver, por ej.*, Patente de los Estados Unidos No. 5.023.252, incorporada aquí a modo de referencia). Dichos parches pueden construirse para administración continua, pulsátil o a demanda

de los agentes farmacéuticos.

Puede ser deseable o necesario introducir la composición farmacéutica al paciente a través de un dispositivo de administración mecánica. La construcción y el uso de dispositivos de administración mecánica de los agentes farmacéuticos se conoce en el arte. Por ejemplo, las técnicas directas para administrar un fármaco directamente al cerebro usualmente incluyen la colocación de un catéter para administración del fármaco en el sistema ventricular del paciente para atravesar la barrera hematoencefálica. Uno de dichos sistemas de administración implantables, usados para el transporte de agentes a las regiones específicas del cuerpo, se describe en la Patente de los Estados Unidos No. 5.011.472, incorporada aquí a modo de referencia.

Las composiciones de la invención pueden contener, además, otros ingredientes de formación de compuestos convencionales aceptables desde el punto de vista farmacéutico, referidos generalmente como vehículos o diluyentes, según se necesite o se desee. Cualesquiera de las composiciones de esta invención pueden preservarse con el agregado de un antioxidante tal como ácido ascórbico o mediante otros preservantes apropiados. Pueden utilizarse procedimientos convencionales para preparar dichas composiciones en formas farmacéuticas apropiadas.

Los ingredientes farmacéuticos comúnmente utilizados que pueden usarse como apropiados para formular la composición para su vía de administración pretendida incluyen: agentes acidulantes, por ejemplo, sin carácter limitativo, acético ácido, ácido cítrico, ácido fumárico, ácido clorhídrico, ácido nítrico; y agentes alcalinizantes tales como, sin carácter limitativo, solución de amoníaco, carbonato de amonio, dietanolamina, monoetanolamina, hidróxido de potasio, borato de sodio, carbonato de sodio, hidróxido de sodio, trietanolamina, trolamina.

Otros ingredientes farmacéuticos incluyen, por ejemplo, sin carácter limitativo, adsorbentes (por ej., celulosa en polvo y carbón activado); propelentes en aerosol (por ej., dióxido de carbono, CCl_2F_2, $F_2ClC\text{-}CClF_2$ y $CClF_3$); agentes de desplazamiento del aire (por ej., nitrógeno y argón); preservantes antifúngicos (por ej., ácido benzoico, butilparabeno,

etilparabeno, metilparabeno, propilparabeno, benzoato de sodio); preservantes antimicrobianos (por ej., cloruro de benzalconio, cloruro de bencetonio, alcohol bencílico, cloruro de cetilpiridinio, clorbutanol, fenol, alcohol feniletílico, nitrato fenilmercúrico y timerosal); antioxidantes (por ej., ácido ascórbico, palmitato de ascorbilo, hidroxianisol butilado, hidroxitolueno butilado, ácido hipofosforoso, monotioglicerol, propil galato, ascorbato de sodio, bisulfito de sodio, sulfoxilato formaldehído de sodio, metabisulfito de sodio); materiales aglutinantes (por ej., polímeros de bloqueo, caucho sintético y natural, poliacrilatos, poliuretanos, siliconas y copolímeros de estireno-butadieno); agentes reguladores de pH (por ej., metafosfato de potasio, fosfato de potasio monobásico, acetato de sodio, citrato de sodio anhidro y citrato de sodio dihidrato); agentes transportadores (por ej., jarabe de acacia, jarabe aromático, elixir aromático, jarabe de cerezas, jarabe de cacao, jarabe de naranjas, jarabe, aceite de maíz, aceite mineral, aceite de maní, aceite de sésamo, inyección bacteriostática de cloruro de sodio y agua bacteriostática para inyección); agentes quelantes (por ej., edetato de disodio y ácido edético); colorantes (por ej., FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramelo y rojo óxido de hierro); agentes aclarantes (por ej., bentonita); agentes emulsionantes (sin carácter limitativo, acacia, cetomacrogol, alcohol cetílico, gliceril monostearato, lecitina, monooleato sorbitano, estearato de polietileno 50); agentes encapsulantes (por ej., gelatina y acetato de celulosa, ftalato); saborizantes (por ej., aceite de anís, aceite de canela, cacao, mentol, aceite de naranja, aceite de menta, y vainillina); humectantes (por ej., glicerina, propilenglicol y sorbitol); agentes de pulverización (por ej., aceite mineral y glicerina); aceites (por ej., aceite de arachis, aceite mineral, aceite de oliva, aceite de maní, aceite de sésamo y aceite vegetal); bases para ungüentos (por ej., lanolina, ungüento hidrofílico, ungüento de polietilenglicol, vaselina, vaselina hidrofílica, ungüento blanco, ungüento amarillo y ungüento de agua de rosas); potenciadores de penetración (administración transdérmica) (por ej., alcoholes monohidroxilados o polihidroxilados, alcoholes grasos saturados o insaturados, ésteres grasos

420.

saturados o insaturados, ácidos dicarboxílicos saturados o insaturados, aceites esenciales, derivados de fosfatidilo, cefalina, terpenos, amidas, éteres, cetonas y ureas); plastificadores (por ej., ftalato de dietilo y glicerina); solventes (por ej., alcohol, aceite de maíz, aceite de semilla de algodón, glicerina, alcohol isopropílico, aceite mineral, ácido oleico, aceite de maní, agua purificada, agua para inyección, agua estéril para inyección, y agua estéril para irrigación); agentes de dureza (por ej., alcohol cetílico, cera de ésteres cetílicos, cera microcristalina, parafina, alcohol estearílico, cera blanca y cera amarilla); bases para supositorios (por ej., manteca de cacao y polietilenglicoles (mezclas)); tensioactivos (por ej., cloruro de benzalconio, nonoxinol 10, oxtoxinol 9, polisorbate 80, lauril sulfato de sodio y monopalmitato sorbitano); agentes de suspensión (por ej., agar, bentonita, carbómeros, carboximetilcelulosa de sodio, hidroxietil celulosa, hidroxipropil celulosa, hidroxipropil metilcelulosa, caolin, metilcelulosa, tragacanto y veegum); edulcorantes por ej., aspartamo, dextrosa, glicerina, manitol, propilenglicol, sacarina de sodio, sorbitol y sacarosa); anti-adherentes para comprimidos (por ej., estearato de magnesio y talco); aglutinantes para comprimidos (por ej., acacia, ácido algínico, carboximetilcelulosa de sodio, azúcar comprimible, etilcelulosa, gelatina, glucosa líquida, metilcelulosa, povidona y almidón pregelatinizado); diluyentes para comprimidos y cápsulas (por ej., fosfato dibásico de calcio, caolin, lactosa, manitol, celulosa microcristalina, celulosa en polvo, carbonato de calcio precipitado, carbonato de sodio, fosfato de sodio, sorbitol y almidón); agentes de recubrimientos de comprimidos (por ej., glucosa líquida, hidroxietil celulosa, hidroxipropil celulosa, hidroxipropil metilcelulosa, metilcelulosa, etilcelulosa, acetato de celulosa, ftalato y lacar); excipientes para compresión directa de comprimidos (por ej., fosfato de calcio dibásico); desintegradores para comprimidos (por ej., ácido algínico, carboximetilcelulosa de calcio, celulosa microcristalina, polacrilin potasio, alginato de sodio, almidón de sodio glicolato, y almidón); deslizantes para comprimidos (por ej., sílice coloidal, almidón de maíz y talco); lubricantes para comprimidos (por ej., estearato de calcio, estearato de magnesio, aceite mineral, ácido esteárico y estearato de zinc); opacantes

421

para comprimidos/ cápsulas (por ej., dióxido de titanio); agentes de lustre para comprimidos (por ej., cera carnauba y cera blanca); agentes espesantes (por ej., cera de abejas, alcohol cetílico y parafina); agentes de tonicidad (por ej., dextrosa y cloruro de sodio); agentes que aumentan la viscosidad (por ej., ácido algínico, bentonita, carbómeros, carboximetilcelulosa de sodio, metilcelulosa, povidona, alginato de sodio y tragacanto); y agentes humectantes (por ej., heptadecaetilen oxicetanol, lecitinas, monooleato sorbitano de polietileno, polioxietileno sorbitol monooleato, y estearato de polioxietileno).

Los compuestos identificados por los métodos descritos aquí pueden administrarse como agente farmacéutico único o combinado con uno o más agentes farmacéuticos adicionales donde la combinación no produce efectos adversos inaceptables. Por ejemplo, los compuestos de esta invención pueden combinarse con agentes anti-obesidad conocidos, o con agentes antidiabéticos conocidos o agentes para otras indicaciones, y similares, como también con sus mezclas y combinaciones.

Los compuestos identificados por los métodos descritos aquí pueden utilizarse, además, en forma de base libre o en composiciones, en investigación y diagnóstico, o como estándares de referencia analítica, y similares. Por consiguiente, la presente invención incluye composiciones que están formadas por un vehículo inerte y una cantidad efectiva de un compuesto identificados por los métodos descritos aquí, o una de sus sales o uno de sus ésteres. Un vehículo inerte es cualquier material que no interactúa con el compuesto que debe transportarse y que brinda soporte, medio de transporte, granel, material rastreable, y similares al compuesto que debe transportarse. Una cantidad efectiva de compuesto es aquella cantidad que produce un resultado o ejerce una influencia sobre el procedimiento particular realizado.

Las formulaciones apropiadas para administración subcutánea, endovenosa, intramuscular y similares; vehículos farmacéuticos apropiados; y técnicas para la formulación y administración pueden prepararse a través de cualquier método conocido en el arte (*ver, por ej.*, Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 20th edición, 2000).

ACTIVIDAD BIOLÓGICA DE LOS COMPUESTOS

Para comprender mejor esta invención, se incluyen los siguientes ejemplos. Estos ejemplos tienen sólo fines ilustrativos y no se construyen como límite del alcance de la invención bajo ningún concepto. Todas las publicaciones mencionadas aquí se incorporan a modo de referencia en su totalidad.

La demostración de la actividad de los compuestos de la presente invención puede lograrse a través de evaluaciones *in vitro*, *ex vivo*, e *in vivo* que son conocidas en el arte. Por ejemplo, para demostrar la eficacia de un agente farmacéutico para el tratamiento de la obesidad y trastornos relacionados, pueden utilizarse los siguientes ensayos.

Evaluación del Efecto del Compuesto sobre la Inhibición de la Actividad Enzimática de DGAT-1

Se aisló el gen DGAT-1 humano (*ver, por ej.*, Patente de los Estados Unidos No. 6.100.077) de una biblioteca de ADNc humano por PCR. Se construyó baculovirus AcNPV recombinante en el cual se reemplazó el gen para la polihedrina de la proteína formadora de cuerpos de oclusión con el gen DGAT-1. Se insertó la secuencia del gen DGAT-1 en el genoma de AcNPV circundante a la posición 3' de la secuencia promotora de polihedrina colocando a DGAT-1 bajo el control de trascripción del promotor de polihedrina. Se infectaron células de insectos Sf9 derivadas de Spodoptera frugiperda con baculovirus recombinante que contenía DGAT-1 a la multiplicidad de infección de 5 y se cosecharon 48 h después de la infección. Se homogeneizaron las células de insectos que expresaban DGAT-1 en Tris 10 mM, sacarosa 250 mM, pH 7,5 a la concentración de 100 mg de biomasa de células húmedas por ml. Se centrifugó el homogenato a 25.000 g durante 30 minutos. Se descartó el pellet de 25.000 g y se centrifugó el sobrenadante a 100.000 g durante 1 h. Se descartó el sobrenadante de 100.000 g y se suspendió nuevamente el pellet de 100.000 g de la membrana que contenía el DGAT-1 en Tris 10 mM, 50% (v/v) de glicerol pH 7,5.

Se determinó la actividad enzimática de DGAT-1 a través de un protocolo de repartición de fases. Específicamente, se incubaron las membranas que contenían DGAT-1 en buffer de didecanoil glicerol 20 mM, ^{14}C-decanoil-CoA 5 mM, $MgCl_2$ 2 mM, 0,04% de BSA, HEPES 20 mM, pH 7,5 en presencia de concentraciones variables de inhibidores. Las evaluaciones se realizaron en volúmenes de 100 µl en placas de microtitulación de 96 pocillos a 0,5 µg de

423.

proteína total de la membrana por pocillo. La valoración se inició con el sustrato y se mezcló suavemente durante 1 h a temperatura ambiente. Se desactivó la actividad con el agregado de 25 µl de solución de ácido fosfórico al 0,1%. La extracción selectiva del producto hidrofóbico tridecanoilglicerol se logró con el agregado de 150 µl de fase que contenía fluido para centelleo Microscint® (Packard, Inc.) y mezclado vigoroso durante 30 minutos. La cuantificación del producto se logró con un contador de centelleo MicroBeta® (Wallac, Inc.) luego de reposar durante aproximadamente 16 h a temperatura ambiente.

Evaluación del Efecto del Compuesto sobre la Inhibición de la Deposición de Triglicéridos Celulares

La valoración basada en células para DGAT-1 se condujo con células de adenocarcinoma colo-rectal humano HT-29 (HTB-38, ATCC). Se cultivaron células HT-29 en placa de 75 cm^2 hasta que hubo ~90% de confluencia en medio DMEM con FBS al 10%, PSF, glutamina, y acetato 10 mM. Luego se colocaron las células en placas nuevamente en placas de 24 pocillos para dar una dilución de 1:1,2 y se cultivaron durante aproximadamente 16 h. Se estimó la formación de triglicéridos con el agregado de ácido láurico al 0,01% en su concentración final en presencia de concentraciones variables de inhibidores. Luego de 6 h, se liberaron las células de la placa con tripsina, se recolectaron por centrifugado, se re-suspendieron en agua, se transfirieron a HPLC de vidrio, se congelaron a -70°C, y se liofilizaron. Se re-suspendieron los pellets celulares congelados en 150 µl de tetrahidrofurano grado HPLC y se sellaron en los vials. Se sonicaron los vials durante 30 minutos con calor en un baño de agua para sonicación (Fisher, Inc.). Se cuantificaron los triglicéridos celulares por HPLC (HP1100, Agilent, Inc.) utilizando detección difracción de luz evaporativa (PL-ELS 1000, Polimer Labs, Inc.). Se logró la separación cromatográfica con un 30 a 100% de buffer B en 4 minutos seguido de 3 minutos a 100% de buffer B usando una columna PLRP S 100 (5 micrones, 150 X 4,6 mm, Polimer Labs, Inc.) a 50°C (A: 50% de acetonitrilo, 2,5% de metanol, B: 100% de tetrahidrofurano). Las inyecciones de las muestras fueron de 20 µl y el detector se fijó a 0,4 SLM, nebulizador a 40°C y evaporador a 80°C. Se

424 424.

identificaron los ácidos grasos no polares y los lípidos de glicerol y se cuantificaron mediante el uso de estándares comerciales.

Evaluación de la Eficacia del Compuesto sobre la Reducción del Peso Corporal en Ratones Obesos Inducidos a Dieta

La finalidad de este protocolo es determinar el efecto de la administración crónica de un compuesto sobre el peso corporal de ratones engordados por exposición a una dieta con alto contenido de grasas a un 45% kcal/g durante un período superior a 10 semanas. El peso corporal de los ratones seleccionados para estos estudios fue superior a las tres desviaciones estándar del peso de un grupo de control de ratones alimentados con alimento estándar para ratones con bajo contenido de grasas (5-6% de grasas). Los animales obesos inducidos con dieta (OID) se han utilizado con frecuencia en la determinación de la eficacia del compuesto en la reducción del peso corporal (*ver, por ej.*, 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).

Este modelo de animales se ha utilizado con éxito en la identificación y caracterización del perfil de eficacia de los compuestos que se usan o se han usado en el manejo del peso corporal en humanos obesos (*ver, por ej.*, Brown, et al., 2001; Guerre-Millo, et al., 2000; Han, et al., 1999).

Un estudio típico incluyó 60-80 ratones C57bl/J6 macho (n = 10/grupo de tratamiento) con un peso corporal promedio de aproximadamente 45 g. Se mantuvieron los ratones en habitaciones estándar para animales con temperatura y humedad controladas y un ciclo de luz/ oscuridad de 12 horas/ 12 horas. Tenían continuamente agua y alimento. Se colocaron los ratones en forma individual. Luego se administró a los animales una dosis falsa de vehículo durante por lo menos cuatro días antes de registrar las mediciones basales de dos días del peso corporal y el consumo de agua y alimento durante 24 horas. Se asignaron los ratones a uno de 6-8 grupos de tratamiento en base a sus pesos corporales en el momento basal. Se establecieron los grupos de modo tal que el error estándar y promedio de 1 peso corporal fueran similares.

425

Se realizó gavage oral a los animales (5 mL/kg) diariamente antes de la fase oscura del ciclo de luz/ oscuridad durante un número predeterminado de días (normalmente 8-14 días) con su dosis/ compuesto asignados. Se midieron el peso corporal, y el consumo de alimento y agua. Se analizaron los datos usando las estadísticas apropiadas siguiendo el diseño de la investigación. El día final, se sacrificó a los animales por inhalación de CO_2.

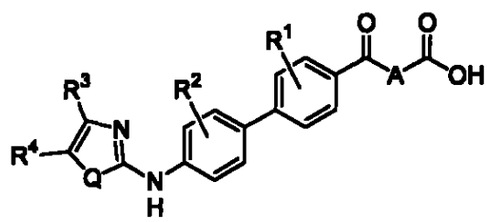
Normalmente se dosificó los compuestos 5 o 10 mg/kg p.o. q.d. como suspensión en 50:50 PEG/Agua, o p.o. b.i.d. como suspensión en 0,5% de metilcelulosa, y se consideró que los compuestos eran activos si se observaba una reducción estadísticamente significativa en el peso corporal para los animales tratados luego de un período de tratamiento de por lo menos siete días, con relación a los animales de control tratados con vehículo.

Las estructuras, los materiales, las composiciones y los métodos descritos aquí pretenden ser ejemplos representativos ejemplos de la invención, y se comprenderá que el alcance de la invención no se limita con el alcance de los ejemplos. Aquellos expertos en el arte reconocerán que la invención puede practicarse con variaciones sobre las estructuras, los materiales, las composiciones y los métodos revelados, y dichas variaciones se consideran dentro del ámbito de la invención.

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo.

1. Un compuesto de Fórmula (I)

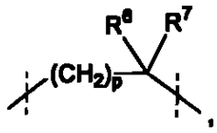


(I)

en el cual

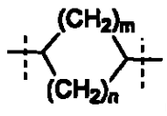
Q es O, S, o NR^5;

A es una ligadura seleccionada de



en la cual p es 1 o 2

y



en la cual m es 0 y n es 1, 2, 3, o 4,

o

m es 1 y n es 1, 2, o 3,

y

en el cual dicha ligadura está sustituida en forma opcional por uno o dos grupos R^6;

R^1 y R^2 se seleccionan en forma independiente de hidrógeno, halo, alquilo (C_1-C_6), y alcoxi (C_1-C_6);

R^3 se selecciona de

hidrógeno,

alquilo (C_1-C_6) sustituido en forma opcional por hidroxi,

y

427 477

fenilo sustituido en forma opcional con alquilo (C_1-C_6), alcoxi (C_1-C_6), o halo;

R^4 se selecciona de hidrógeno, nitro, y alquilo (C_1-C_6);

o

R^3 y R^4 pueden, cuando se los toma junto con los átomos de carbono a los cuales están unidos, formar un anillo de benceno sustituido en forma opcional con hasta dos sustituyentes seleccionados de

halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), nitro, ciano, haloalquilo (C_1-C_6), haloalcoxi (C_1-C_6), aminocarbonilo, alquilo (C_1-C_6)aminocarbonilo, bis[alquilo (C_1-C_6)]aminocarbonilo, aminosulfonilo, alquil (C_1-C_6) aminosulfonilo, bis[alquilo (C_1-C_6)]aminosulfonilo, (C_1-C_6)alquilcarbonilamino, alquil (C_1-C_6) sulfonilamino, hidroxi-alquil (C_2-C_6) aminocarbonilo, 1-morfolinilcarbonilo, y 1-piperidinilcarbonilo,

y

cuando dos de dichos sustituyentes del anillo de benceno son alquilo (C_1-C_6) y están unidos a átomos de carbono adyacentes del anillo de benceno, pueden unirse para formar un anillo carbocíclico de 5-7 miembros;

R^5 es hidrógeno o alquilo (C_1-C_6);

R^6 es hidrógeno;

R^7 es hidrógeno

o

alquilo (C_1-C_6) sustituido en forma opcional con

alcoxi (C_1-C_6),

bis[alquil (C_1-C_3)]amino

o

fenilo sustituido en forma opcional con halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), o ciano;

o

R^6 y R^7 son ambos alquilo (C_1-C_6);

o

R^6 y R^7 pueden formar, junto con el átomo de carbono al cual están unidos,

un anillo carbocíclico de 3 a 5 miembros,

o

428

un anillo de 6 miembros representado por



en el cual W es CH_2, $C(CH_3)_2$, O, NR^9, S, o SO_2;

R^8 es alquilo (C_1-C_6);

y

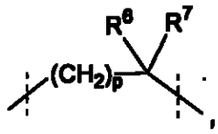
R^9 es hidrógeno o alquilo (C_1-C_6);

o sus sales y ésteres aceptables desde el punto de vista farmacéutico.

2. El compuesto de la reivindicación 1, en el cual

Q es NR^5;

A es



en la cual p es 1 o 2,

y

en el cual dicha ligadura está sustituida en forma opcional por uno o dos grupos R^8;

R^3 y R^4 pueden, cuando se los toma junto con los átomos de carbono a los cuales están unidos, formar un anillo de benceno sustituido en forma opcional con hasta dos sustituyentes seleccionados de

halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), nitro, ciano, haloalquilo (C_1-C_6), haloalcoxi (C_1-C_6), aminocarbonilo, alquil (C_1-C_6)aminocarbonilo, bis[alquilo (C_1-C_6)]aminocarbonilo, aminosulfonilo, alquil (C_1-C_6) aminosulfonilo, bis[alquilo (C_1-C_6)]aminosulfonilo, (C_1-C_6)alquilcarbonilamino, alquil (C_1-C_6) sulfonilamino, hidroxi-(C_2-C_6)alquilaminocarbonilo, 1-morfolinilcarbonilo, y 1-piperidinilcarbonilo; y

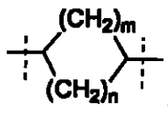
R^1, R^2, R^5, R^6, R^7, R^8, R^9, y W son como se los definió en la reivindicación 1.

3. El compuesto de la reivindicación 1, en el cual

Q es NR^5;

A es

429



en la cual m es 0 y n es 1, 2, 3, o 4,

o

m es 1 y n es 1, 2, o 3,

y

en el cual dicha ligadura está sustituida en forma opcional por uno o dos grupos R^6;

R^3 y R^4 pueden, cuando se los toma junto con los átomos de carbono a los cuales están unidos, formar un anillo de benceno sustituido en forma opcional con hasta dos sustituyentes seleccionados de

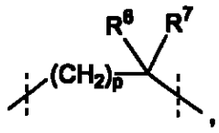
halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), nitro, ciano, haloalquilo (C_1-C_6), haloalcoxi (C_1-C_6), aminocarbonilo, alquil (C_1-C_6)aminocarbonilo, bis[alquilo (C_1-C_6)]aminocarbonilo, aminosulfonilo, alquil (C_1-C_6) aminosulfonilo, bis[alquilo (C_1-C_6)]aminosulfonilo, (C_1-C_6)alquilcarbonilamino, alquil (C_1-C_6) sulfonilamino, hidroxi-(C_2-C_6)alquilaminocarbonilo, 1-morfolinilcarbonilo, y 1-piperidinilcarbonilo; y

R^1, R^2, R^5, y R^8 son como se los definió en la reivindicación 1.

4. El compuesto de la reivindicación 1, en el cual

Q es O;

A es



en la cual p es 1 o 2,

y

en el cual dicha ligadura está sustituida en forma opcional por uno o dos grupos R^6;

R^3 y R^4 pueden, cuando se los toma junto con los átomos de carbono a los cuales están unidos, formar un anillo de benceno sustituido en forma opcional con hasta dos sustituyentes seleccionados de

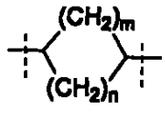
halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), nitro, ciano, haloalquilo (C_1-C_6), haloalcoxi (C_1-C_6), aminocarbonilo, alquil (C_1-C_6)aminocarbonilo, bis[alquilo (C_1-C_6)]aminocarbonilo, aminosulfonilo, alquil (C_1-C_6) aminosulfonilo, bis[alquilo (C_1-C_6)]aminosulfonilo, (C_1-C_6)alquilcarbonilamino, alquil (C_1-C_6) sulfonilamino, hidroxi-(C_2-C_6)alquilaminocarbonilo, 1-morfolinilcarbonilo, y 1-piperidinilcarbonilo; y

R^1, R^2, R^6, R^7, R^8, R^9, y W son como se los definió en la reivindicación 1.

5. El compuesto de la reivindicación 1, en el cual

Q es O;

A es



en la cual m es 0 y n es 1, 2, 3, o 4,

o

m es 1 y n es 1, 2, o 3,

y

en el cual dicha ligadura está sustituida en forma opcional por uno o dos grupos R^6;

R^3 y R^4 pueden, cuando se los toma junto con los átomos de carbono a los cuales están unidos, formar un anillo de benceno sustituido en forma opcional con hasta dos sustituyentes seleccionados de

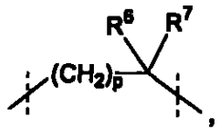
halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), nitro, ciano, haloalquilo (C_1-C_6), haloalcoxi (C_1-C_6), aminocarbonilo, alquil (C_1-C_6)aminocarbonilo, bis[alquilo (C_1-C_6)]aminocarbonilo, aminosulfonilo, alquil (C_1-C_6) aminosulfonilo, bis[alquilo (C_1-C_6)]aminosulfonilo, (C_1-C_6)alquilcarbonilamino, alquil (C_1-C_6) sulfonilamino, hidroxi-(C_2-C_6)alquilaminocarbonilo, 1-morfolinilcarbonilo, y 1-piperidinilcarbonilo; y

R^1, R^2, y R^8 son como se los definió en la reivindicación 1.

6. El compuesto de la reivindicación 1, en el cual

Q es S;

A es



en la cual p es 1 o 2,

y

en el cual dicha ligadura está sustituida en forma opcional por uno o dos grupos R^6;

R^3 y R^4 pueden, cuando se los toma junto con los átomos de carbono a los cuales están unidos, formar un anillo de benceno sustituido en forma opcional con hasta dos sustituyentes seleccionados de

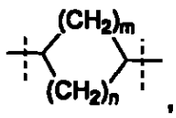
halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), nitro, ciano, haloalquilo (C_1-C_6), haloalcoxi (C_1-C_6), aminocarbonilo, alquil (C_1-C_6)aminocarbonilo, bis[alquilo (C_1-C_6)]aminocarbonilo, aminosulfonilo, alquil (C_1-C_6) aminosulfonilo, bis[alquilo (C_1-C_6)]aminosulfonilo, (C_1-C_6)alquilcarbonilamino, alquil (C_1-C_6) sulfonilamino, hidroxi-(C_2-C_6)alquilaminocarbonilo, 1-morfolinilcarbonilo, y 1-piperidinilcarbonilo; y

R^1, R^2, R^6, R^7, R^8, R^9, y W son como se los definió en la reivindicación 1.

7. El compuesto de la reivindicación 1, en el cual

Q es S;

A es



en la cual m es 0 y n es 1, 2, 3, o 4,

o

m es 1 y n es 1, 2, o 3,

y

en el cual dicha ligadura está sustituida en forma opcional por uno o dos grupos R^6;

R^3 y R^4 pueden, cuando se los toma junto con los átomos de carbono a los cuales están unidos, formar un anillo de benceno sustituido en forma opcional con hasta dos sustituyentes seleccionados de

halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), nitro, ciano, haloalquilo (C_1-C_6), haloalcoxi (C_1-C_6), aminocarbonilo, alquil (C_1-C_6)aminocarbonilo, bis[alquilo (C_1-C_6)]aminocarbonilo, aminosulfonilo, alquil (C_1-C_6) aminosulfonilo, bis[alquilo (C_1-C_6)]aminosulfonilo, (C_1-C_6)alquilcarbonilamino, alquil (C_1-C_6) sulfonilamino, hidroxi-(C_2-C_6)alquilaminocarbonilo, 1-*morfolinilcarbonilo*, y 1-*piperidinilcarbonilo*; y

R^1, R^2, y R^8 son como se los definió en la reivindicación 1.

8. El compuesto de la reivindicación 1 seleccionado del grupo formado por:

ácido 4-[4'-(1H-bencimidazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoico;

ácido 4-{4'-[(5-metoxi-1H-bencimidazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico;

ácido *trans*-2-{[4'-(1H-bencimidazol-2-ilamino)-1,1'-bifenil-4-il]carbonil}ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(5-metoxi-1H-bencimidazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-[(4'-{[5-(trifluorometil)-1H-bencimidazol-2-il]amino}-1,1'-bifenil-4-il)carbonil] ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(5,6-difluoro-1H-bencimidazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-{[4'-(1H-bencimidazol-2-ilamino)-3'-fluoro-1,1'-bifenil-4-il]carbonil}ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({3'-fluoro-4'-[(5-metoxi-1H-bencimidazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico; y

433 435.

ácido *trans*-(1R,2R)-2-[(3'-fluoro-4'-{[5-(trifluorometil)-1H-bencimidazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico.

9. El compuesto de la reivindicación 1 seleccionado del grupo formado por:

Ácido 4-[4'-(1,3-benzoxazol-2-ilamino)-1,1'-bifenil-4-il]-4-oxo-2-(2-feniletil)butanoico;

ácido 2,2-dimetil-4-{4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico;

ácido 4-{4'-[(6-cloro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico;

ácido 4-{4'-[(6-metoxi-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico;

ácido 2,2-dimetil-4-{4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico;

ácido 2,2-dimetil-4-{4'-[(4-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico;

ácido 2,2-dimetil-4-oxo-4-[4'-(5,6,7,8-tetrahidronaphtho[2,3-d][1,3]oxazol-2-ilamino)-1,1'-bifenil-4-il]butanoico;

ácido 4-{4'-[(5-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico;

ácido 4-{4'-[(5-isopropil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico;

ácido 2,2-dimetil-4-oxo-4-{4'-[(5-propil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}butanoico;

ácido *trans*-2-({4'-[(6-cloro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(6-metoxi-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-

il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(5-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(5,6-dimetil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-{[4'-(1,3-benzoxazol-2-ilamino)-1,1'-bifenil-4-il]carbonil}ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(5-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(6-cloro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-[(4'-{[5-(trifluorometil)-1,3-benzoxazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(6-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1S,2S)-2-({4'-[(6-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-

435

il}carbonil) ciclohexan-carboxílico;

ácido *trans*-2-({4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclohexan-carboxílico;

ácido 4-{4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxo-2-(2-feniletil) butanoico;

ácido *trans*-2-({3'-fluoro-4'-[(6-metoxi-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(6-cloro-1,3-benzoxazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({3'-fluoro-4'-[(5-fluoro-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({3'-fluoro-4'-[(6-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({3'-fluoro-4'-[(5-metil-1,3-benzoxazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico; y

ácido *trans*-(1R,2R)-2-[(3'-fluoro-4'-{[5-(trifluorometil)-1,3-benzoxazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico.

10. El compuesto de la reivindicación 1 seleccionado del grupo formado por:

ácido 4-[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2,2-dimetil-4-oxobutanoico;

ácido 4-{4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico;

ácido 4-{4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico;

436.

ácido 2,2-dimetil-4-oxo-4-[4'-(1,3-tiazol-2-ilamino)-1,1'-bifenil-4-il]butanoico;

ácido 4-[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]-2-(2-metoxietil)-4-oxobutanoico;

ácido 4-{4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2-(2-metoxietil)-4-oxobutanoico;

ácido 4-{4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2-(2-metoxietil)-4-oxobutanoico;

ácido *trans*-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclobutan-carboxílico;

ácido *trans*-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido 4-{4'-[(5-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico;

ácido 2,2-dimetil-4-{4'-[(6-nitro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico;

ácido 4-{4'-[(4-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico;

ácido *trans*-(1R,2R)-2-{[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]carbonil} ciclopentan-carboxílico;

ácido *trans*-2-{[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]carbonil}ciclopentan-carboxílico;

ácido 4-{4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxo-2-(2-feniletil) butanoico;

ácido 2-(2-{4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2-oxoetil)pentanoico;

437.

ácido *trans*-2-({4'-[(5-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(6-nitro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(4-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido 4-{4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2-[2-(dimetilamino) etil]-4-oxobutanoico;

ácido 2-[2-(dimetilamino)etil]-4-{4'-[(5-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico;

ácido 2-[2-(dimetilamino)etil]-4-{4'-[(6-nitro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico;

ácido *trans*-2-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(6-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(6-etoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1S,2S)-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido 2,2-dimetil-4-{4'-[(5-nitro-1,3-tiazol-2-il)amino]-1,1'-bifenil-4-il}-4-oxobutanoico;

438.

ácido 4-(4'-{[4-(4-clorofenil)-1,3-tiazol-2-il]amino}-1,1'-bifenil-4-il)-2,2-dimetil-4-oxobutanoico;

ácido *trans*-(1R,2R)-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1S,2S)-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *cis*-3-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclohexan-carboxílico;

ácido *cis*-3-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclohexan-carboxílico;

ácido *trans*-2-[(4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(6-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1S,2S)-2-({4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1S,2S)-2-({4'-[(6-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(5-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-[(4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(5-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(5,7-dimetil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-[(4'-{[6-(metilsulfonil)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(5,6-dimetil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido 4-{4'-[(6-etoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico;

ácido 4-{4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}-2,2-dimetil-4-oxobutanoico;

ácido *trans*-2-({4'-[(5,7-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopropan-carboxílico;

ácido *trans*-(1R,2R)-2-[(4'-{[5-(trifluorometil)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico;

ácido *trans*-2-{[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]carbonil}ciclopropan-carboxílico;

ácido *trans*-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclohexan-carboxílico;

ácido *trans*-2-({4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopropan-carboxílico;

ácido *trans*-2-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopropan-carboxílico;

ácido *trans*-2-({4'-[(5,7-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopropan-carboxílico;

ácido *trans*-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclopropan-carboxílico;

ácido *trans*-2-{[4'-(1,3-benzotiazol-2-ilamino)-1,1'-bifenil-4-il]carbonil}ciclobutan-carboxílico;

ácido *trans*-2-({4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclobutan-carboxílico;

ácido *trans*-2-({4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil) ciclobutan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico;

ácido *trans*-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-2-({3'-fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({3'-fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico;

ácido *trans*-2-{[4'-(1,3-benzotiazol-2-ilamino)-3'-fluoro-1,1'-bifenil-4-il]carbonil} ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

441 441

ácido *trans*-(1S,2S)-2-({4'-[(4,6-difluoro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-[(3'-fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({3'-fluoro-4'-[(5-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({3'-fluoro-4'-[(4-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(5-cloro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({3'-fluoro-4'-[(6-metil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(5,7-dimetil-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-({4'-[(5,7-difluoro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il} carbonil)ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-[(3'-fluoro-4'-{[5-(trifluorometil)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico;

ácido *trans*-(1R,2R)-2-[(3'-fluoro-4'-{[6-(trifluorometoxi)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico;

ácido *trans*-2-({3'-fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclobutan-carboxílico;

ácido *trans*-2-{[4'-(1,3-benzotiazol-2-ilamino)-3'-fluoro-1,1'-bifenil-4-il]carbonil} ciclobutan-carboxílico;

ácido *trans*-2-{[4'-(1,3-benzotiazol-2-ilamino)-3'-fluoro-1,1'-bifenil-4-il]carbonil} ciclopropan-carboxílico;

ácido *trans*-2-({3'-fluoro-4'-[(6-metoxi-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il} carbonil)ciclopropan-carboxílico;

ácido *trans*-(1R,2R)-2-({3'-fluoro-4'-[(6-isopropil-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

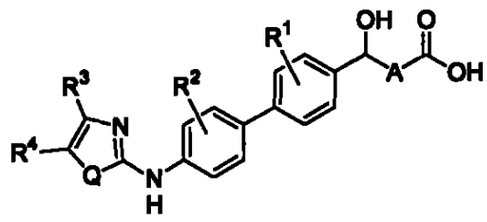
ácido *trans*-2-({3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-1,1'-bifenil-4-il}carbonil)ciclopentan-carboxílico;

ácido *trans*-2-[(3'-fluoro-4'-{[6-(trifluorometil)-1,3-benzotiazol-2-il]amino}-1,1'-bifenil-4-il)carbonil]ciclopentan-carboxílico;

ácido 4-{4'-[(6-cloro-1,3-benzotiazol-2-il)amino]-3'-fluoro-1,1'-bifenil-4-il}-4-oxo-2-(2-feniletil)butanoico; y

ácido (1R,2R)-2-[{3'-fluoro-4'-[(6-fluoro-1,3-benzotiazol-2-il)amino]-bifenil-4-il}(hidroxi)metil]ciclopentancarboxílico.

11. Un compuesto de Fórmula (Ia)

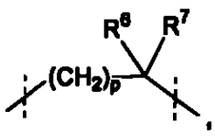


(Ia)

en el cual

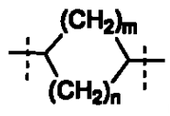
Q es O, S, o NR^5;

A es una ligadura seleccionada de



en la cual p es 1 o 2

y



en la cual m es 0 y n es 1, 2, 3, o 4,

o

m es 1 y n es 1, 2, o 3,

y

en el cual dicha ligadura está sustituida en forma opcional con uno o dos grupos R^6;

R^1 y R^2 se seleccionan en forma independiente de hidrógeno, halo, alquilo (C_1-C_6), y alcoxi (C_1-C_6);

R^3 se selecciona de

hidrógeno,

alquilo (C_1-C_6) sustituido en forma opcional con hidroxi,

y

fenilo sustituido en forma opcional con alquilo (C_1-C_6), alcoxi (C_1-C_6), o halo;

R^4 se selecciona de hidrógeno, nitro, y alquilo (C_1-C_6);

o

R^3 y R^4 pueden, cuando se los toma junto con los átomos de carbono a los cuales están unidos, formar un anillo de benceno sustituido en forma opcional con hasta dos sustituyentes seleccionados de

halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), nitro, ciano, haloalquilo (C_1-C_6), haloalcoxi (C_1-C_6), aminocarbonilo, alquil (C_1-C_6)aminocarbonilo, bis[alquilo (C_1-C_6)]aminocarbonilo, aminosulfonilo, alquil (C_1-C_6) aminosulfonilo, bis[alquilo (C_1-C_6)]aminosulfonilo, alquilcarbonilamino(C_1-C_6), alquil (C_1-C_6) sulfonilamino, hidroxi-alquilaminocarbonilo(C_2-C_6), 1-morfolinilcarbonilo, y 1-piperidinilcarbonilo,

y

cuando dos de dichos sustituyentes del anillo de benceno son alquilo (C_1-C_6) y están unidos a átomos de carbono adyacentes del anillo de benceno, pueden unirse para formar un anillo carbocíclico de 5-7 miembros;

R^5 es hidrógeno o alquilo (C_1-C_6);

R^6 es hidrógeno;

444

R^7 es hidrógeno

o

alquilo (C_1-C_6) sustituido en forma opcional con

alcoxi (C_1-C_6),

bis[alquil (C_1-C_3)]amino

o

fenilo sustituido en forma opcional con halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), o ciano;

o

R^6 y R^7 son ambos alquilo (C_1-C_6);

o

R^6 y R^7 pueden formar, junto con el átomo de carbono al cual están unidos,,

un anillo carbocíclico de 3 a 5 miembros,

o

un anillo de 6 miembros representado por



en el cual W es CH_2, $C(CH_3)_2$, O, NR^9, S, o SO_2;

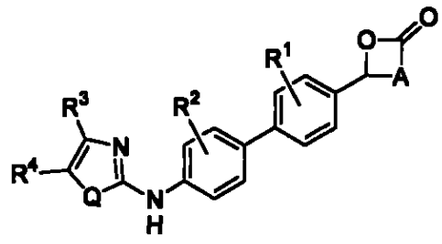
R^8 es alquilo (C_1-C_6);

y

R^9 es hidrógeno o alquilo (C_1-C_6);

o sus sales y ésteres farmacéuticos.

12. Un compuesto de Fórmula (Ib)

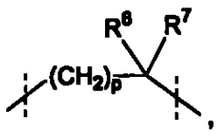


(Ib)

en el cual

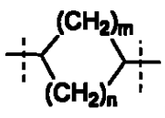
Q es O, S, o NR^5;

A es una ligadura seleccionada de



en la cual p es 1 o 2

y



en la cual m es 0 y n es 1, 2, 3, o 4,

o

m es 1 y n es 1, 2, o 3,

y

en el cual dicha ligadura está sustituida en forma opcional con uno o dos grupos R^6;

R^1 y R^2 se seleccionan en forma independiente de hidrógeno, halo, alquilo (C_1-C_6), y alcoxi (C_1-C_6);

R^3 se selecciona de

hidrógeno,

alquilo (C_1-C_6) sustituido en forma opcional con hidroxi,

y

fenilo sustituido en forma opcional con alquilo (C_1-C_6), alcoxi (C_1-C_6), o halo;

R^4 se selecciona de hidrógeno, nitro, y alquilo (C_1-C_6);

o

R^3 y R^4 pueden, cuando se los toma junto con los átomos de carbono a los cuales están unidos, formar un anillo de benceno sustituido en forma opcional con hasta dos sustituyentes seleccionados de

halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), nitro, ciano, haloalquilo (C_1-C_6), haloalcoxi (C_1-C_6), aminocarbonilo, alquil (C_1-C_6)aminocarbonilo, bis[alquilo (C_1-C_6)]aminocarbonilo, aminosulfonilo, alquil (C_1-C_6) aminosulfonilo, bis[alquilo (C_1-C_6)]aminosulfonilo, (C_1-C_6)alquilcarbonilamino,

alquil (C_1-C_6) sulfonilamino, hidroxi-alquilaminocarbonilo(C_2-C_6),

1-morfolinilcarbonilo, y 1-piperidinilcarbonilo,

y

cuando dos de dichos sustituyentes del anillo de benceno son alquilo (C_1-C_6) y están unidos a átomos de carbono adyacentes del anillo de benceno, pueden unirse para formar un anillo carbocíclico de 5-7 miembros;

R^5 es hidrógeno o alquilo (C_1-C_6);

R^6 es hidrógeno;

R^7 es hidrógeno

o

alquilo (C_1-C_6) sustituido en forma opcional con

alcoxi (C_1-C_6),

bis[alquil (C_1-C_3)]amino

o

fenilo sustituido en forma opcional con halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), o ciano;

o

R^6 y R^7 son ambos alquilo (C_1-C_6);

o

R^6 y R^7 pueden formar, junto con el átomo de carbono al cual están unidos,

un anillo carbocíclico de 3 a 5 miembros,

o

un anillo de 6 miembros representado por



en el cual W es CH_2, $C(CH_3)_2$, O, NR^9, S, o SO_2;

R^8 es alquilo (C_1-C_6);

y

R^9 es hidrógeno o alquilo (C_1-C_6);

o sus sales y ésteres farmacéuticos.

13. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1, o una sal o un éster aceptables desde el punto de vista farmacéutico, en combinación con un vehículo aceptable desde el punto de vista farmacéutico.

14. Una composición farmacéutica que comprende una cantidad terapéuticamente

efectiva de un compuesto de la reivindicación 1, o una de sus sales o uno de sus ésteres aceptables desde el punto de vista farmacéutico, en combinación con un vehículo aceptable desde el punto de vista farmacéutico y uno o más agentes farmacéuticos.

15. La composición farmacéutica de la reivindicación 14, en el cual dicho agente farmacéutico es un agente anti-obesidad seleccionado del grupo formado por agonistas β-3, antagonistas CB-1, inhibidores del neuropéptido Y5, supresores del apetito, e inhibidores de lipasa.

16. La composición farmacéutica de la reivindicación 14, en el cual dicho agente farmacéutico es un agente para el tratamiento de la diabetes seleccionado del grupo formado por insulina, derivados de la insulina, ligandos PPAR, fármacos de sulfonilurea, inhibidores de α-glucosidasa, biguanidas, inhibidores de PTP-1B, inhibidores de DPP-IV, inhibidores de 11-beta-HSD, GLP-1 y derivados de GLP-1, GIP y derivados de GIP, PACAP y derivados de PACAP, y secretina y derivados de secretina.

17. La composición farmacéutica de la reivindicación 14, en el cual dicho agente farmacéutico es un agente para el tratamiento de trastornos lipídicos seleccionado del grupo formado por inhibidores de HMG-CoA, ácido nicotínico, compuestos reductores de ácidos grasos, fármacos reductores de lípidos, inhibidores de ACAT, secuestradores de bilis, inhibidores de la recaptación de ácido biliar, inhibidores del transporte triglicéridos microsomales, y derivados de ácido fíbrico.

18. La composición farmacéutica de la reivindicación 14, en el cual dicho agente farmacéutico es un agente anti-hipertensivo seleccionado del grupo formado por bloqueadores β, bloqueadores del canal de calcio, diuréticos, inhibidores de renina, inhibidores de ACE, antagonistas del receptor AT-1, antagonistas del receptor ET, y nitratos.

19. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 8, 9, 10, 11, o 12, o una sal o un éster aceptables desde el punto de vista farmacéutico, en combinación con un vehículo aceptable desde el punto de vista farmacéutico.

20. Una composición farmacéutica que comprende una cantidad terapéuticamente

448
448

efectiva de un compuesto de la reivindicación 8, 9, 10, 11, o 12, o una de sus sales o uno de sus ésteres aceptables desde el punto de vista farmacéutico, en combinación con un vehículo aceptable desde el punto de vista farmacéutico y uno o más agentes farmacéuticos.

21. Un método de tratamiento de la obesidad que comprende el paso de administrar a un sujeto que lo necesita una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 o una composición de la reivindicación 13.

22. Un método de inducir la pérdida de peso que comprende el paso de administrar a un sujeto que lo necesita una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 o una composición de la reivindicación 13.

23. Un método para prevenir el aumento de peso que comprende el paso de administrar a un sujeto que lo necesita una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 o una composición de la reivindicación 13.

24. Un método de tratamiento de trastornos relacionados con la obesidad que comprende el paso de administrar a un sujeto que lo necesita una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 o una composición de la reivindicación 13.

25. El método de la reivindicación 24, en el cual dicho trastorno relacionado con la obesidad se selecciona del grupo formado por dislipidemia, colesterol, cálculos vesiculares, afección de la vesícula, gota, cáncer, anormalidades menstruales, infertilidad, ovarios poliquísticos, osteopatía degenerativa, apnea del sueño, hipertrigliceridemia, Síndrome X, diabetes tipo 2, enfermedades ateroescleróticas, hiperlipidemia, hipercolesteremia, niveles bajos de HDL, hipertensión, enfermedad cardiovascular, enfermedad cardíaca coronaria, arteriopatía coronaria, enfermedad cerebrovascular, accidente cerebrovascular, y enfermedad de los vasos periféricos.

26. Un método de tratamiento de la obesidad que comprende el paso de administrar a un sujeto que lo necesita una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 en combinación con uno o más agentes farmacéuticos.

449
449

27. El método de la reivindicación 26, en el cual el compuesto de la reivindicación 1 y uno o más agentes farmacéuticos se administran como una formulación de dosificación farmacéutica única.

28. Un método de tratamiento de la obesidad que comprende el paso de administrar a un sujeto que lo necesita una cantidad terapéuticamente efectiva de una composición de la reivindicación 14, 15, 16, 17, o 18.

29. Un método de tratamiento de trastornos relacionados con la obesidad que comprende el paso de administrar a un sujeto que lo necesita una cantidad terapéuticamente efectiva de una composición de la reivindicación 14, 15, 16, 17, o 18.

30. Compuestos de acuerdo con la reivindicación 1 para el tratamiento y/o la profilaxis de la obesidad y trastornos relacionados con la obesidad.

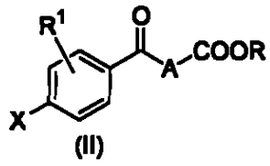
31. Medicamento que contiene por lo menos un compuesto de acuerdo con la reivindicación 1 en combinación con por lo menos un vehículo o excipiente aceptable desde el punto de vista farmacéutico, farmacéuticamente seguro.

32. Uso de compuestos de acuerdo con la reivindicación 1 para la fabricación de un medicamento para el tratamiento y/o la profilaxis de la obesidad y trastornos relacionados con la obesidad.

33. Medicamentos de acuerdo con la reivindicación 31 para el tratamiento y/o la profilaxis de la obesidad.

34. Un proceso para la preparación de un compuesto de Fórmula (VIII) que comprende los pasos de:

hacer reaccionar un compuesto de Fórmula (II)



(II)

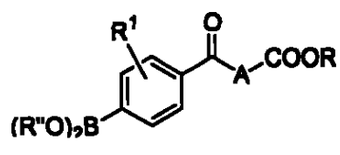
en el cual

R es hidrógeno o alquilo (C_1-C_6);

X es Cl, Br, o I; y

R^1 y A son como se los definió en la reivindicación 1;

con un reactivo de éster de ácido bórico para dar un compuesto de Fórmula (X)



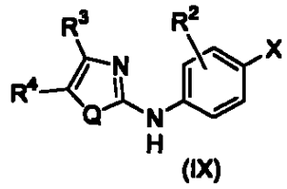
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en el cual

R es hidrógeno o alquilo (C_1-C_6); y

R^1 y A son como se los definió en la reivindicación 1;

y acoplar el compuesto de Fórmula (X) con un compuesto de Fórmula (IX)

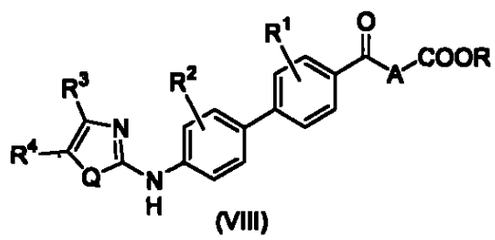


(IX)

en el cual

R^2, R^3, R^4, y Q son como se los definió en la reivindicación 1;

en presencia de un catalizador de paladio, y en forma opcional en presencia de una base, para dar el compuesto de Fórmula (VIII)



(VIII)

en el cual

R es hidrógeno o alquilo (C_1-C_6),

R^1, R^2, R^3, R^4, A, y Q son como se los definió en la reivindicación 1.

35. El método de la reivindicación 34, en el cual el reactivo de éster de ácido bórico es pinacol borano y la base es carbonato de potasio.

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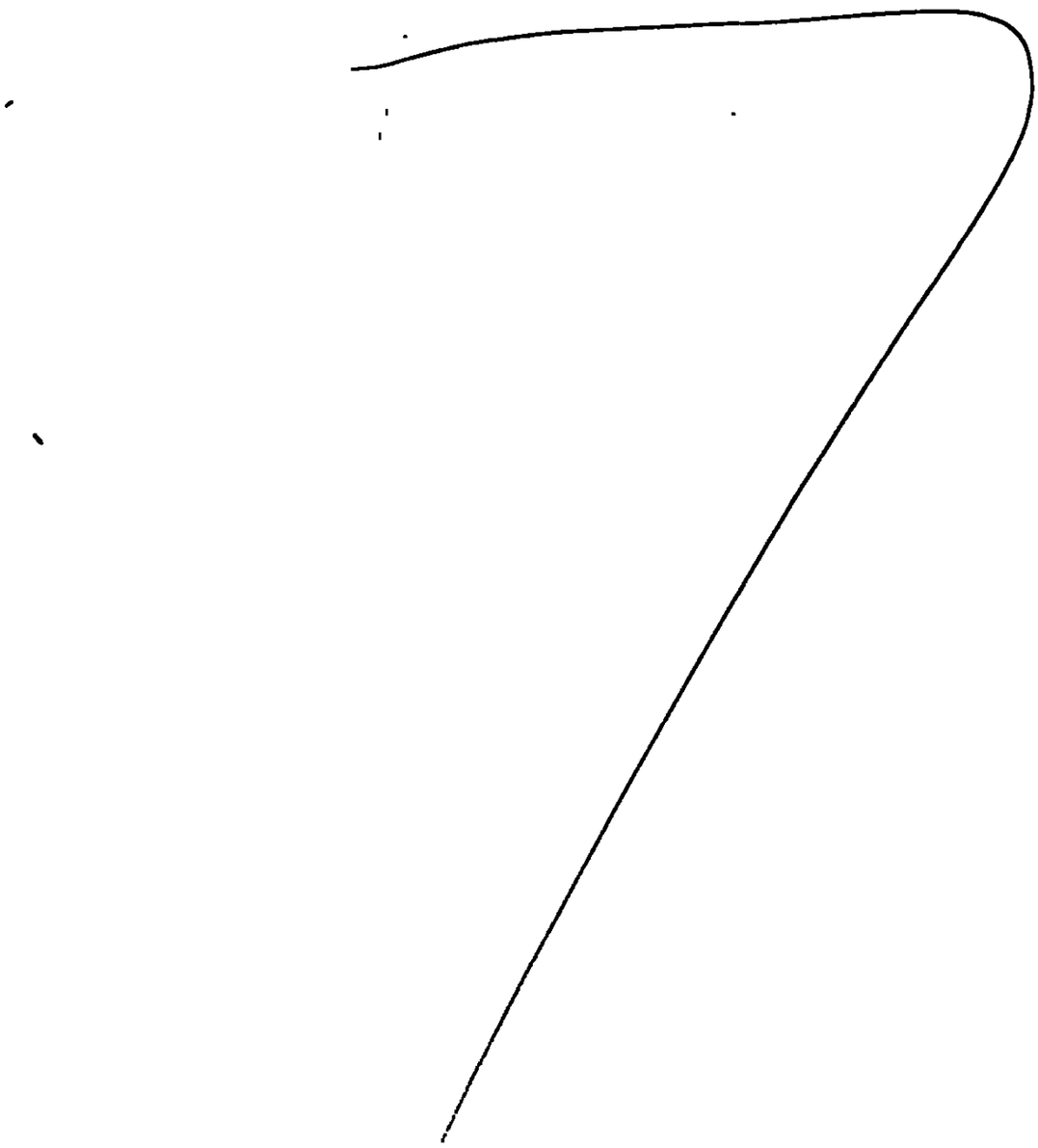
451

RESUMEN

Esta invención se refiere a ciertos compuestos de ácido alquilarílico, composiciones, y métodos para tratar o prevenir la obesidad y enfermedades relacionadas.

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(30) Priority Data:
60/469,619 9 May 2003 (09.05.2003) US

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

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): SMITH, Roger [US/US]; 65 Winterhill Road, Madison, CT 06443 (US). CAMPBELL, Ann-Marie [US/US]; 69 Lynn Drive, Monroe, CT 06468 (US). COISH, Philip [CA/US]; 548 Orange Street, Suite 401, New Haven, CT 06511 (US). DAI, Miao [CN/US]; 83-72 Daniels Street, Briarwood, NY 11435 (US). JENKINS, Susan [US/US]; 50 Bolt Lane, Milford, CT 06460 (US). LOWE, Derek [US/US]; 31 Bittersweet Lane, Hamden, CT 06518 (US). O'CONNOR, Stephen [US/US]; 977 Little Meadow Road, Guilford, CT 06437 (US). SU, Ning [CN/US]; 121 October Hill Road, Hamden, CT 06518 (US). WANG, Gan [CN/US]; 5 Cassella Drive, Wallingford, CT 06492 (US). ZHANG, Minghao [CN/US]; 75 Nyselius Place, Stamford, CT 06905 (US). ZHU, Lei [US/US]; 101 Oak Ridge Lane, Milford, CT 06460 (US).

(74) Agents: GREENMAN, Jeffrey, M. et al.; Bayer Pharmaceuticals Corporation, 400 Morgan Lane, West Haven, CT 06516 (US).

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

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

(88) Date of publication of the international search report:
3 February 2005

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

WO 2004/100881 A3

(54) Title: PREPARATION AND USE OF ARYL ALKYL ACID DERIVATIVES FOR THE TREATMENT OF OBESITY

(57) Abstract: This invention relates to certain aryl alkyl acid compounds, compositions, and methods for treating or preventing obesity and related diseases.

453

453

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/14036

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 235/30; A61K 31/4168
US CL : 548/307.4; 514/395
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. : 548/307.4; 514/395

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)
STN Database Online; FILE REG, FILE CAPLUS; EAST; WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,110,939 A (JANSSENS et al) 29 August 2000 (29.08.2000), columns 27-35 Table 1.	8

☐ 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" 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

Date of the actual completion of the international search	Date of mailing of the international search report
01 October 2004 (01.10.2004)	18 NOV 2004
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. (703) 305-3230	Authorized officer Janet L Coppins Telephone No. (571) 272-1600

Form PCT/ISA/210 (second sheet) (January 2004)

~~454~~
454

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/14036

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.: 1-7 and 9-35
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.:
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 an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/14036

Continuation of Box II Reason 2:
In these claims, the numerous variables (e.g. R1-R9, A, Q, W, n, m, p, etc), their voluminous complex meanings, their seemingly endless permutations and combinations make it virtually 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 made on the first discernable invention in the claims, which is the first named compound of claim 8.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 5161-PCT	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US04/14036	International filing date (*day/month/year*) 06 May 2004 (06.05.2004)	(Earliest) Priority Date (*day/month/year*) 09 May 2003 (09.05.2003)
Applicant BAYER PHARMACEUTICALS CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the Report**
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      ☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.
2. ☒ Certain claims were found unsearchable (See Box No. II)
3. ☐ Unity of invention is lacking (See Box No. III)
4. With regard to the title,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. ____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/14036

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.: 1-7 and 9-35
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.:
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 an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

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

458

458

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/14036

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 235/30; A61K 31/4168
US CL : 548/307.4; 514/395
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. : 548/307.4; 514/395

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)
STN Databases Online; FILE REG, FILE CAPLUS; EAST; WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,110,939 A (JANSSENS et al) 29 August 2000 (29.08.2000), columns 27-35 Table I.	8

☐ 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
"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

Date of the actual completion of the international search 01 October 2004 (01.10.2004)	Date of mailing of the international search report 18 NOV 2004
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. (703) 305-3230	Authorized officer Janet L. Coppins J. Roberts for Telephone No. (571) 272-1600

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/14096

Continuation of Box II Reason 2:
In these claims, the numerous variables (e.g. R1-R9, A, Q, W, n, m, p, etc), their voluminous complex meanings, their seemingly endless permutations and combinations make it virtually 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 made on the first discernable invention in the claims, which is the first named compound of claim 8.

460.

'ATENT COOPERATION TREATY

PCT/US04/014036

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

GREENMAN, Jeffrey, M.
Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 29 September 2004 (29.09.2004)	
Applicant's or agent's file reference 5161-PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/US04/014036	International filing date *(day/month/year)* 06 May 2004 (06.05.2004)
International publication date *(day/month/year)*	Priority date *(day/month/year)* 09 May 2003 (09.05.2003)
Applicant BAYER PHARMACEUTICALS CORPORATION et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)* An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
09 May 2003 (09.05.2003)	60/469,619	US	19 August 2004 (19.08.2004)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 740 14 35

Authorized officer
Cruz Juan

Facsimile No. +41 22 338 89 65
Telephone No. +41 22 338 8239

5161-PCT

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.162)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	5161-PCT
I	Title of Invention	PREPARATION AND USE OF ARYL ALKYL ACID DERIVATIVES FOR THE TREATMENT OF OBESITY
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name:	BAYER PHARMACEUTICALS CORPORATION
II-5	Address:	400 Morgan Lane West Haven, Connecticut 06516 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	(203) 812-6450
II-9	Facsimile No.	(203) 812-6459
III-1	Applicant and/or Inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	SMITH, Roger
III-1-5	Address:	65 Winterhill Road Madison, Connecticut 06443 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	CAMPBELL, Ann-Marie
III-2-5	Address:	69 Lynn Drive Monroe, Connecticut 06468 United States of America
III-2-6	State of nationality	US
III-2-7	State of residence	US
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	COISH, Philip
III-3-5	Address:	548 Orange Street Suite 401 New Haven, Connecticut 06511 United States of America
III-3-6	State of nationality	CA
III-3-7	State of residence	US
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	DAI, Miao
III-4-5	Address:	83-72 Daniels Street Briarwood, New York 11435 United States of America
III-4-6	State of nationality	CN
III-4-7	State of residence	US
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	JENKINS, Susan
III-5-5	Address:	50 Bolt Lane Milford, Connecticut 06460 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US

463.
463

PCT REQUEST

Original (for SUBMISSION)

III-6	Applicant and/or Inventor	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	LOWE, Derek
III-6-5	Address:	31 Bittersweet Lane Hamden, Connecticut 06518 United States of America
III-6-6	State of nationality	US
III-6-7	State of residence	US
III-7	Applicant and/or Inventor	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	O'CONNOR, Stephen
III-7-5	Address:	977 Little Meadow Road Guilford, Connecticut 06437 United States of America
III-7-6	State of nationality	US
III-7-7	State of residence	US
III-8	Applicant and/or Inventor	
III-8-1	This person is:	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	SU, Ning
III-8-5	Address:	121 October Hill Road Hamden, Connecticut 06518 United States of America
III-8-6	State of nationality	CN
III-8-7	State of residence	US
III-9	Applicant and/or Inventor	
III-9-1	This person is:	applicant and inventor
III-9-2	Applicant for	US only
III-9-4	Name (LAST, First)	WANG, Gan
III-9-5	Address:	5 Cassella Drive Wallingord, Connecticut 06492 United States of America
III-9-6	State of nationality	CN
III-9-7	State of residence	US

III-10	Applicant and/or inventor	
III-10-1	This person is:	applicant and inventor
III-10-2	Applicant for	US only
III-10-4	Name (LAST, First)	ZHANG, Mingbao
III-10-5	Address:	75 Nyselius Place Stamford, Connecticut 06905 United States of America
III-10-6	State of nationality	CN
III-10-7	State of residence	US
III-11	Applicant and/or inventor	
III-11-1	This person is:	applicant and inventor
III-11-2	Applicant for	US only
III-11-4	Name (LAST, First)	ZHU, Lei
III-11-5	Address:	101 Oak Ridge Lane Milford, Connecticut 06460 United States of America
III-11-6	State of nationality	US
III-11-7	State of residence	US
IV-1	Agent or common representative; or address for correspondence	
	The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	GREENMAN, Jeffrey, M.
IV-1-2	Address:	Bayer Pharmaceuticals Corporation 400 Morgan Lane West Haven, Connecticut 06516 United States of America
IV-1-3	Telephone No.	(203) 812-6450
IV-1-4	Facsimile No.	(203) 812-6459
IV-1-5	e-mail	susan.pellegrino.b@bayer.com
IV-1-6	Agent's registration No.	26552
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	GRAY,William, F.(31018); CHIU,Jerrie, L.(41670); PELLEGRINO,Susan, M.(48972); SHIMEI,Barbara, A.(29862)

5161-PCT

PCT REQUEST

Original (for SUBMISSION)

V	DESIGNATIONS		
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.		
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	09 May 2003 (09.05.2003)	
VI-1-2	Number	60/469,619	
VI-1-3	Country	US	
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	1	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

VIII-4-1	Declaration: Inventorship (only for the purposes of the designation of the United States of America) Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to the international application of which it forms a part (if filing declaration with application). I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications", by application number, country or Member of the World Trade Organization, day, month, and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
VIII-4-1-1	Prior applications:	

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name (LAST, First)	SMITH, Roger
VIII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	Madison, Connecticut
VIII-4-1-1-3	Mailing address:	65 Winterhill Road Madison, CT 06443 United States of America
VIII-4-1-1-4	Citizenship:	US
VIII-4-1-1-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

5161-PCT

8/13

PCT REQUEST

Original (for SUBMISSION)

VIII-4-1-2-1	Name (LAST, First)	CAMPBELL, Ann-Marie
VIII-4-1-2-2	Residence: (city and either US State, if applicable, or country)	Monroe, Connecticut
VIII-4-1-2-3	Mailing address:	69 Lynn Drive Monroe, CT 06468 United States of America
VIII-4-1-2-4	Citizenship:	US
VIII-4-1-2-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-2-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-3-1	Name (LAST, First)	COISH, Philip
VIII-4-1-3-2	Residence: (city and either US State, if applicable, or country)	New Haven, Connecticut
VIII-4-1-3-3	Mailing address:	548 Orange Street Suite 401 New Haven, CT 06511 United States of America
VIII-4-1-3-4	Citizenship:	CA
VIII-4-1-3-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-3-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

469
469

PCT REQUEST

Original (for SUBMISSION)

VIII-4-1-4-1	Name (LAST, First)	DAI, Miao
VIII-4-1-4-2	Residence: (city and either US State, if applicable, or country)	Briarwood, New York
VIII-4-1-4-3	Mailing address:	83-72 Daniels Street Briarwood, NY 11435 United States of America
VIII-4-1-4-4	Citizenship:	CN
VIII-4-1-4-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-4-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-5-1	Name (LAST, First)	JENKINS, Susan
VIII-4-1-5-2	Residence: (city and either US State, if applicable, or country)	Milford, Connecticut
VIII-4-1-5-3	Mailing address:	50 Bolt Lane Milford, CT 06460 United States of America
VIII-4-1-5-4	Citizenship:	US
VIII-4-1-5-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-5-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

5161-PCT

10/13

PCT REQUEST

Original (for SUBMISSION)

VIII-4-1-6-1	Name (LAST, First)	LOWE, Derek
VIII-4-1-6-2	Residence: (city and either US State, if applicable, or country)	Hamden, Connecticut
VIII-4-1-6-3	Mailing address:	31 Bittersweet Lane Hamden, CT 06518 United States of America
VIII-4-1-6-4	Citizenship:	US
VIII-4-1-6-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-6-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-7-1	Name (LAST, First)	O'CONNOR, Stephen
VIII-4-1-7-2	Residence: (city and either US State, if applicable, or country)	Guilford, Connecticut
VIII-4-1-7-3	Mailing address:	977 Little Meadow Road Guilford, CT 06437 United States of America
VIII-4-1-7-4	Citizenship:	US
VIII-4-1-7-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-7-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

5161-PCT

11/13

PCT REQUEST

Original (for SUBMISSION)

VIII-4-1-8-1	Name (LAST, First)	SU, Ning
VIII-4-1-8-2	Residence: (city and either US State, if applicable, or country)	Hamden, Connecticut
VIII-4-1-8-3	Mailing address:	121 October Hill Road Hamden, CT 06518 United States of America
VIII-4-1-8-4	Citizenship:	CN
VIII-4-1-8-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-8-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-9-1	Name (LAST, First)	WANG, Gan
VIII-4-1-9-2	Residence: (city and either US State, if applicable, or country)	Wallingord, Connecticut
VIII-4-1-9-3	Mailing address:	5 Cassella Drive Wallingord, CT 06492 United States of America
VIII-4-1-9-4	Citizenship:	CN
VIII-4-1-9-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-9-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

VIII-4-1-10-1	Name (LAST, First)	ZHANG, Mingbao
VIII-4-1-10-2	Residence: (city and either US State, if applicable, or country)	Stamford, Connecticut
VIII-4-1-10-3	Mailing address:	75 Nyselius Place Stamford, CT 06905 United States of America
VIII-4-1-10-4	Citizenship:	CN
VIII-4-1-10-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-10-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-11-1	Name (LAST, First)	ZHU, Lei
VIII-4-1-11-2	Residence: (city and either US State, if applicable, or country)	Milford, Connecticut
VIII-4-1-11-3	Mailing address:	101 Oak Ridge Lane Milford, CT 06460 United States of America
VIII-4-1-11-4	Citizenship:	US
VIII-4-1-11-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-11-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

5161-PCT

13/13

PCT REQUEST

Original (for SUBMISSION)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	13	✓
IX-2	Description	161	-
IX-3	Claims	23	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	198	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	PELLEGRINO, Susan, M.	
X-1-2	Name of signatory		
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/US
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

5161-PCT

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	

0-4	Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet				
0-4-1	Prepared Using		PCT-SAFE [EASY mode] Version 3.50 (Build 0002.162)		
0-9	Applicant's or agent's file reference		5161-PCT		
2	Applicant		BAYER PHARMACEUTICALS CORPORATION		
12	Calculation of prescribed fees		fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee	T	⇨	300	
12-2-1	Search fee	S	⇨	1000	
12-2-2	International search to be carried out by		US		
12-3	International filing fee (first 30 sheets)	I1	1134		
12-4	Remaining sheets		168		
12-5	Additional amount	(X)	12		
12-6	Total additional amount	I2	2016		
12-7	I1 + I2 =	I	3150		
12-12	EASY Filing reduction	R	-81		
12-13	Total international filing fee (I-R)	I	⇨	3069	
12-14	Fee for priority document Number of priority documents requested		1		
12-15	Fee per document	(X)	20		
12-16	Total priority document fee:	P	⇨	20	
12-17	TOTAL FEES PAYABLE (T+S+I+P)		⇨	4389	
12-19	Mode of payment		authorization to charge deposit account		
12-20	Deposit account instructions The receiving Office		United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	Authorization to charge the total fees indicated above.		✓		
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.		✓		
12-20-3	Authorization to charge the fee for priority document.		✓		
12-21	Deposit account No.		13-3372		
12-22	Date		05 May 2004 (05.05.2004)		
12-23	Name and signature		PELLEGRINO, Susan, M.		

476

475

SUPERINDUSTRIA Y COMERCIO
Radicacion : [illegible]
Fecha (AMD): 2005-12-07 17:27:24 Folios: 476
Tramite : 011 PCJ-PATENT 379 FASE NAL1 411 PRESENTAL
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 87,655
FECHA : NOVIEMBRE 15 DE 2005

***** 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	27496710	15/11/2005	56,100,000.00

***** 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	443,000.00
		TOTAL : $	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo 14125-841-010-1

Extracto publicación
Folio 475

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SUPERINDUSTRIA Y COMERCIO
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Fecha (AMD): 2005-12-07 17:27:24
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	(✓)
- Indicacion de que se solicita la concesión de una patente	( )	(✓)
- Datos de identificacion del solicitante o de la persona que se presenta la solicitud	( )	(✓)
- Descripcion de la invención	( )	(✓)
- Dibujos de ser estos pertinentes.	( )	(✓)
Comprobante de Pago de las tasas establecidas		
COMPLETA (✓) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificacion del solicitante o de la persona que presenta	(✓)	( )
- la solicitud		
- Representacion gráfica o fotografica del Diseño Industrial o muestra del Material que incorpora el diseño	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicacion de que 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 de trazado	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable